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POSTOPERATIVE CARE AFTER CARDIOPULMONARY BYPASS FOR OPEN HEART SURGERY*

ROBERT S. CARTWRIGHT, M.D., AND GEORGE J. MAGOVERN, M.D.

Albuquerque, New Mexico, and Pittsburgh, Pennsylvania

Survival following open heart surgery is in a large measure dependent upon the proficiency of postoperative care. Observations on more than 100 patients undergoing correction of intracardiac defects have led to formulation of principles of management which have been lifesaving on numerous occasions. Since minor variations assume significance when superimposed on an often markedly abnormal physiologic state, standard methods of care must be applied assiduously.

In addition, special measures have been devised to cope with complex problems.

HYPERVOLEMIA, HYPOVOLEMIA AND CARDIAC FAILURE

Early in the development of our pump-oxygenator techniques, it became evident that the central venous pressure was a major aid in maintaining constant blood volume during bypass and surgery. The additional value of this body parameter as a guide to blood replacement during the postoperative period was immediately obvious.

Hypervolemia, hypovolemia and cardiac failure are states requiring differentiation. In the presence of a low or normal venous pressure one may liberally transfuse for the correction of hypotension or signs suggestive of incipient shock. In fact, our clinical experience indicates that the first reliable objective evidence of hypovolemia is a fall in the central venous pressure. On the other hand, a notably elevated venous pressure indicates hypervolemia or cardiac failure and in either case phlebotomy is often wise.

Since insertion of a polyethylene catheter into the right atrium is easily attained during right or bilateral thoracotomy or by electrocardiographic control before surgery, we have utilized this method of evaluation in noncardiac as well as cardiac patients. The value of this modality has been the subject of a separate report.[9] However, reliable pressures may ordinarily be obtained through a cannula in the inferior vena cava. In adults a number 280 polyethylene catheter is inserted through a cutdown in the greater saphenous vein at the femoral triangle. The outer end of the tube is connected through a Clay-Adams adapter and a three-way stopcock to a vertical plastic tube ($^3/_{16}$-inch inner diameter or an ordinary manometer) with a level being used to establish the zero point at the height of the midaxillary line.

Donald and Moffitt,[5] Mendelsohn and associates[13] and others[2] have also found the central venous pressure a helpful index of circulating blood volume. The following case, although not one involving open heart surgery, is clearly illustrative.

CASE 1

This case was reported in detail elsewhere.[9] J. R., a 56-year-old white man, underwent left pneumonectomy for carcinoma on October 22, 1958.

* From the Departments of Thoracic Surgery of the Allegheny General Hospital and the University of Pittsburgh School of Medicine and the Department of Cardiovascular Surgery, Lovelace Clinic and Foundation for Medical Education and Research, Albuquerque.

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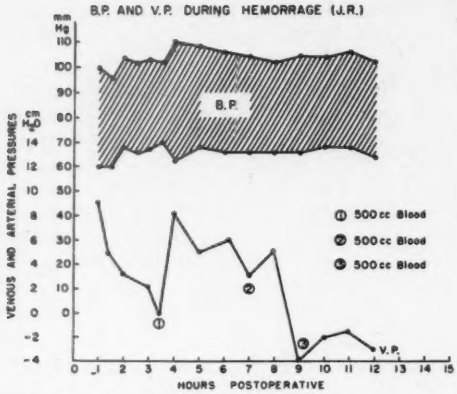

FIG. 1. Case 1. Pressure recordings demonstrate marked fall in right atrial pressure during blood loss.

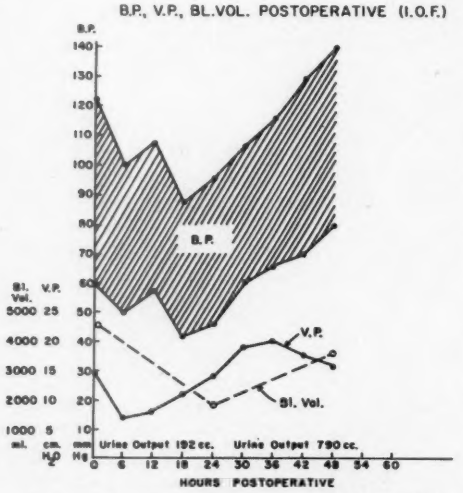

FIG. 2. Case 2. Pressure recordings and blood volume determinations demonstrate rising venous pressure in presence of falling blood volume with favorable response to transfusion although a 20 cm./H_2O venous pressure was accepted. This atypical response has been noted in occasional patients with known impaired myocardial function.

Blood loss at surgery was 1200 ml. with 1500 ml. blood replacement. During the first 12 postoperative hours, pulse and arterial blood pressure remained relatively constant. However, severe decreases in right atrial pressure occurred (fig. 1). Although the arterial systolic pressure was maintained between 95 and 100 mm. Hg during the first 40 hours postoperatively, the patient required 24 units of whole blood with replacement given solely on the basis of the atrial pressure. Blood volume* at the end of the second postoperative day was 4150 ml. (350 ml. deficit from preoperative level).

On occasion, we have found it necessary to accept moderate elevation of the central venous pressure while correcting obvious hypovolemia. Apparently, ventricular function is at times partially impaired but still sufficient to maintain life during essential blood transfusion (fig. 2). Most patients in this category have had acquired heart disease with known deficiencies of the myocardium.

CASE 2

I. O. F., a 49-year-old white man, was admitted to Allegheny General Hospital on August 5, 1958. He had had angina and shortness of breath for one year. At the age of 25 he had rheumatic fever.

Physical examination. The blood pressure was 120/70. The peripheral pulses were normal. There were no signs of congestive failure. The left heart border was 1 cm. to the left of the midclavicular line. A_2 was absent. P_2 was diminished. A grade III aortic systolic murmur was present.

Laboratory. The electrocardiogram showed a left bundle branch block. The chest x-ray revealed moderate left ventricular enlargement. Calcification of neither the aortic nor the mitral valve was evident.

Heart catheterization. On August 7, 1958, a combined right and left heart catheterization was performed, revealing an aortic valve orifice of 0.6 cm.^{2} Left ventricular failure was evident by the high end-diastolic pressure.

	mm. Hg
Left atrium	(23)†
Left ventricle	145/6-20
Aorta	96/58
Right atrium	(6)
Right ventricle	44/1-8

Preoperative treatment included digitalis, diuretics, salt restriction and steroids over a two-week period.

Operation. On August 22, 1958, a transaortic commissurotomy was performed with the aid of

* Blood volume determination was carried out utilizing radioactive iodinated serum albumin and substituting a calibrated lead plug for the usual dilution methods.

† Figures in parentheses indicate mean pressures.

extracorporeal circulation. The ascending aorta was exposed through a vertical sternum-splitting incision. The heart was arrested with potassium citrate. The aortic valve orifice was estimated at 0.7 cm.^{2} Moderate calcification was present on two leaflets, and all three commissures were fused. The commissures were incised under direct vision, producing an orifice of 2.7 cm.^{2} Valvular insufficiency was not evident. The procedure was uncomplicated. Total bypass lasted 10 minutes, and partial bypass lasted an additional 12 minutes. A mean arterial pressure of 70 mm. Hg was maintained. When heart action resumed spontaneously, a blood pressure of 120/80 was recorded. A catheter placed into the inferior vena cava was used to monitor the venous pressure during and after surgery.

Postoperative course. Blood loss of 1800 ml. occurred and was replaced during the first 18 hours. The venous pressure varied 7 to 14 cm./H_2O and the arterial pressure 88/40 to 122/60. Urinary output was depressed 192 ml. during this period. Urine pH was 4.5 and blood pH was 7.30. Despite the administration of sodium bicarbonate the patient manifested respiratory as well as laboratory signs of acidosis. The heart rate was slow and regular and the electrocardiogram showed no postoperative change. Blood nonprotein nitrogen was 57.4 mg. per cent, serum sodium 130 mEq./L., chloride 90 mEq./L. and potassium 5.4 mEq./L.

The blood volume was 4500 ml. immediately after operation, compared to a preoperative value of 3000 ml. and an estimated normal of 3700 ml. The blood volume was 1900 ml. 24 hours later. The arterial pressure remained the same and the venous pressure was elevated 12 to 15 cm./H_2O.

Despite the elevated venous pressure, blood replacement was continued during the next 24 hours. The arterial pressure gradually increased to 140/80 and the venous pressure remained 14 to 20 cm./H_2O. The urinary output increased steadily to 790 ml. in 24 hours. The urine showed no free hemoglobin.

By the third postoperative day the blood volume was 3600 ml., the hemoglobin was 13.0 gm. per cent and the hematocrit was 42 per cent. The urinary output returned to normal. The patient had no further serious complications and was discharged from the hospital on September 8, 1958.

Comment. In retrospect, the patient had been excessively dehydrated preoperatively in an attempt to relieve the left ventricular failure. Subsequent transfusions resulted in initial venous hypertension. As soon as the hypovolemia was corrected the urinary output returned to normal.

NEUROLOGIC INJURY

Williams and Spencer[19] were the first to demonstrate the value of prolonged hypothermia in the treatment of patients with central nervous system injury after cardiac arrest. They reported the success of 30 to 34°C. body temperature in alleviating brain damage in four patients having circulatory arrest of three to five minutes. Hypothermia was instituted immediately upon recognition of severe neurologic injury and was maintained for 24 to 72 hours. A moderate neurologic deficit (partial central blindness) persisted in one patient. Stimulated by the material in an abstract of the report by Williams and Spencer, Kent[10] and other members of our group successfully managed a 32-year-old woman with eight minutes of known cardiac arrest following attempted bronchography. Extensor spasm and coma resolved after only 24 hours of 32°C. hypothermia. To our knowledge this is the longest documented period of normothermic circulatory arrest to be followed by recovery. With this success as a background we were led to apply the technique to a patient demonstrating a left hemiplegia after the open heart repair of an atrial septal defect utilizing cardiopulmonary bypass. A complete recovery followed as indicated in this report.

CASE 3

H. A. C., a 31-year-old white man, was admitted to Allegheny General Hospital on April 28, 1958. Two months before admission the patient had consulted his private physician because of cough, fever and malaise. Signs of congestive failure were noted for the first time. There was no previous history of heart disease. Digitalis was started at that time.

Physical examination. Examination on admission revealed a well developed patient with no signs of congestive failure. The left heart border was widened to percussion. P_2 was increased. A grade II systolic murmur was present along the left lower sternal border.

Fluoroscopy showed enlargement of the right atrium and the right ventricle and aneurysmal dilation of the pulmonary artery.

Right heart catheterization had been performed on February 20, 1958, showing an atrial septal defect, pulmonary hypertension and a pulmonary flow 1½ times the peripheral flow.

	O_2 content, vol. %
Left ventricle	20.72
Inferior vena cava	16.55
Superior vena cava	15.12
Right atrium, upper	15.50
Right atrium, lower	17.85
Right ventricle, inflow	17.60
Right ventricle, apex	16.95
Pulmonary artery, main	16.92
Pulmonary artery, right	17.40
Right brachial artery	19.95
Pulmonary vein, right	20.50
Oxygen capacity	21.46

	mm. Hg
Right atrium	(6)
Right ventricle	72/6-9
Pulmonary artery	72/36 (50)
Pulmonary wedge	(5)
Left atrium	(6)
Left ventricle	140/4-6
Right brachial artery	125/81
Cardiac index	3.7 L./min./m.^{2}
Pulmonary index	5.5 L./min./m.^{2}

Operation. On April 30, 1958, the right atrium was explored through a right thoracotomy. A large septal defect was found. With the aid of extracorporeal circulation, the defect was closed with a continuous 2-0 silk suture. Total bypass lasted 35 minutes. The procedure was uncomplicated.

Postoperative course. April 30, 1958. 12:00 p.m.: The patient returned to the recovery room partially reacted from anesthesia. It was noted that the patient did not move the left arm. 9:00 p.m.: The patient had developed a complete left hemiplegia, including seventh nerve paralysis. 11:00 p.m.: Hypothermia was instituted by packing the patient in ice. Temperature, 103° (rectal). A body temperature of 86 to 94° (30 to 34°C.) was maintained during next 60 hours except as indicated. Shivering was avoided by use of a parenteral barbiturate in conjunction with chlorpromazine.

May 1, 1958. 7:00 a.m.: Temperature 96°. Tracheostomy performed.

May 2, 1958. 1:00 a.m.: Patient reacting and coherent, but moving only right extremities. Temperature, 99°. 3:00 a.m.: Temperature, 100°. Generalized convulsion. 8:00 a.m.: Temperature, 91.5°. 10:00 a.m.: Temperature, 86°.

May 3, 1958. 12:00 a.m.: Temperature, 93°. After 12:00 p.m.: Temperature maintained below 100°. The patient was alert and coherent, the facial paralysis had disappeared and there was movement in the left extremities.

May 4, 1958. Surface cooling with ice still required to maintain temperature below 100°. Definite return of function to left extremities.

May 5, 1958. Surface cooling discontinued.

November 1, 1958. (Readmission.) No residual hemiplegia. No shunt detected on recatheterization.

Initially we questioned the probability of cerebral air embolism from the left atrium in the absence of coronary embolism with fibrillation or arrest. Among others Kent and Blades[11] and Geoghegan and Lam[6] have shown a predilection of air injected into the left atrium to enter the coronary circulation. However, when the right posterolateral approach is used with the patient in the left lateral decubitus position, the posterior (noncoronary) aortic cusp is uppermost in the field, and we suspect a significant air mass passed above the coronary orifices in our patient. Our supposition is supported by the demonstration of a residual 5 ml. of air in the right superior pulmonary vein following the repair of an atrial defect in a subsequent patient using the same posterolateral approach. In this position the pulmonary veins, being above the level of the atrium, serve as a bubble trap. This air can probably be expressed by application of positive intrapulmonary pressure by the anesthetist as one ties the final suture closing the septal defect. Since the anterolateral approach gives admirable exposure and avoids the unfavorable lateral position, we have chosen this method of protecting against air trapping.

Although we have not been faced with subsequent examples of air embolism or with the necessity of using prolonged hypothermia following anoxia during an inadequate bypass, the probable value of this form of therapy, if required, seems well established.[20] Increased solubility of gases at lower temperatures may be a significant physical factor accounting for improvement in the event of air embolism.

METABOLIC ACIDOSIS

Metabolic acidosis is a common abnormal state following cardiopulmonary bypass and has been subjected to considerable conjecture and study at both the clinical and experimental levels. Our earliest patients demonstrated acidosis despite our use of high flows (2.0 to 2.2 L./m.^{2}). Studying the factors contributing to this situation, we learned that donor blood collected on the morning

of surgery often stayed in a 37°C. water-bath for a number of hours while awaiting use in the oxygenator. Refrigeration of blood immediately following collection until shortly before its use has been a highly significant measure in preventing notable acidosis in our patients. Acidosis developing in the postoperative period has been reported by several observers. We agree with Pontius and his associates[16] that hypocapnia during surgery and bypass not only masks metabolic acidosis but aggravates the condition. The lactic acidemia developing during respiratory alkalosis appears to be the significant factor involved.

Metabolic acidosis will result when conditions such as respiratory insufficiency or decreased cardiac output, as seen in complete heart block, cause tissue hypoxia. Correction of the underlying difficulty leads to relief of the acidotic state. Although the problem of acidosis has been virtually eliminated on our service, our early experience included several patients with severe acidosis (pH less than 7.10) who were immediately and notably benefited by administration of sodium bicarbonate intravenously. Case 4, reported in detail elsewhere,[3] is an example of this situation.

CASE 4

N. B., a 33-year-old Negro male laborer, underwent direct vision transaortic commissurotomy for acquired aortic stenosis on February 25, 1958, with cardiopulmonary bypass and potassium citrate arrest. Because of difficulties with temporary caval obstruction during bypass an existing mitral stenosis was relieved by finger fracture commissurotomy. Cyanosis associated with mental confusion was prominent in the postoperative period. A pH of 7.01 was obtained and intravenous administration of 270 mEq. of sodium bicarbonate was accompanied by disappearance of cyanosis and improvement of the patient's general condition. Tracheostomy was later necessary to control tracheobronchial secretions. Eventual recovery was complete.

DECREASED RED CELL SURVIVAL

Hewitt and associates[8] observed decreased red cell survival following the use of extracorporeal circulation with length of cell survival being inversely proportional to the total perfusion time. Other observers have detected only minimal hemolysis[1] and still others[4] feel that the resulting anemia is not sufficient to require correction by transfusion.

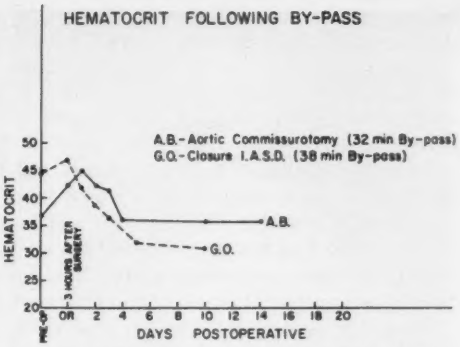

FIG. 3. Decrease in hematocrit during postoperative course after cardiopulmonary bypass in two patients who failed to receive corrective transfusions.

Our own experience indicates that, with the use of the Kay-Cross oxygenator with either Sigmamotor or DeBakey roller (Pemco) pumps, a significant anemia occurs in some patients and that correction by transfusion has at times been advisable. The unfavorable effects of anemia on wound healing and body defense mechanisms as well as the increased incidence of thrombosis and embolism in its presence prompted us to correct significant drops in hematocrit by transfusion with packed red cells.

Figure 3 demonstrates decrease in the circulating red cell mass during the postoperative periods of two patients who failed to receive early correction by transfusion. Neither of these patients demonstrated other sources of blood loss, and constant blood volume during the postoperative period was documented in one (A. B.).

PULMONARY COMPLICATIONS

Pulmonary complications following open heart surgery are at times enigmatic. The major thoracic incisions required undoubtedly contribute to an increased incidence of atelectasis and pneumonia. However, other factors are involved.

Explanations proposed include:

1. Pulmonary vascular stasis in patients with large left to right shunts due to decreased blood flow in the dilated pulmonary vascular bed.[17]

2. Overloading of the pulmonary vascular system due to failure to eliminate left atrial blood in patients with large bronchial artery

flows or in instances of appreciable coronary flows, especially following elective cardiac arrest.[12]

3. Direct damage to pulmonary capillary and alveolar cells by excessive oxygen, desiccation, or other abnormalities created by elimination of pulmonary arterial flow.[7]

Swan and associates[18] feel that patients with large left to right shunts have benefited from anticoagulant therapy following intracardiac surgery under hypothermia. We have not tried this measure. Since pulmonary complications are rare following repair of simple interatrial defects utilizing cardiopulmonary bypass, total circulatory arrest during hypothermia may account for the intravascular thrombosis noted.

Kolff and associates,[12] Muller and associates[14] and Norlander and associates[15] have all emphasized the value of left atrial drainage in preventing overloading of the pulmonary circulation with subsequent postoperative difficulties. Our own experience is not conclusive in this regard although left atrial drainage does aid in repair of tetralogy of Fallot hearts. In other instances withdrawal of the caval cannulas into the right atrium has proved sufficient.

When other measures fail to correct pulmonary insufficiency, tracheostomy and intermittent positive pressure breathing seem helpful in improving oxygen saturation and general patient response. Barnard and associates[2] and Norlander and associates[15] have made similar observations. In addition, the more or less empirical use of steroids has seemed to aid recovery in our group. The following case illustrates some of the problems involved.

CASE 5

M. O. S., a 13-year-old white girl was first admitted to Allegheny General Hospital on July 1, 1958. She was asymptomatic. Cyanosis had never been present. She had good exercise tolerance. Serial x-rays had shown a gradual enlargement of the cardiac silhouette and an increase in vascular markings. A heart murmur had been present since early childhood.

Physical examination. On examination the blood pressure was 130/88. The patient was well developed and slightly obese. A grade III systolic murmur was heard best in the left second interspace and was transmitted over the precordium to the axilla. P_2 was increased. M_1 was decreased. A grade I apical diastolic murmur was present. There were no signs of congestive failure.

Right heart catheterization. On July 2, 1958, a right heart catheterization was performed showing an atrial septal defect and mild pulmonary artery hypertension.

	O_2 content, vol. %
Inferior vena cava	12.62
Superior vena cava	12.11
Right atrium, upper	11.93
Right atrium, lower	14.72
Right ventricle, inflow	14.87
Right ventricle, outflow	15.51
Pulmonary artery, main	14.68
Pulmonary artery, left	14.87
Right brachial artery	17.20
Pulmonary vein, right	17.68
Oxygen capacity	18.35

	mm. Hg
Right atrium	(10)
Right ventricle	72/5-11
Pulmonary artery	41/17 (26)
Cardiac output	5.3 L./min.
Pulmonary flow	10.58 L./min.
Cardiac index	3.1 L./min./m.^{2}
Pulmonary index	6.1 L./min./m.^{2}

The electrocardiogram showed delayed atrioventricular conduction and a right bundle branch block. The x-ray was consistent with enlargement of the right ventricle, the left ventricle and the left atrium.

Operation. On August 13, 1958, a right thoracotomy was performed and the right atrium digitally explored. A septal defect of the ostium primum type was present. Both mitral and tricuspid valves were intact. With the aid of extracorporeal circulation the defect was repaired utilizing a Teflon patch. Bypass lasted 105 minutes. Arterial flow was 4500 ml./min. Mean arterial pressure was 70 mm. Hg. During the procedure, the lungs were intermittently inflated with 100 per cent oxygen.

Postoperative period. During the first 24 hours after operation the systemic pressure varied from 110/60 to 130/90. The venous pressure ranged from 7 to 13 cm. H_2O. The temperature rose to 103° (rectal). The urinary output was 15 to 45 ml./hr. The heart rate was regular at 74 to 104/min.

On the second postoperative day a nodal tachycardia developed. Venous pressure remained normal. Despite increased digitalization, the tachycardia persisted into the third 24-hour period. The temperature remained elevated and bilateral basal rales were present. Cyanosis and labored respirations were present. The chest x-ray showed diffuse, patchy infiltration throughout both lung fields (fig. 4*A*). Steroid therapy was begun.

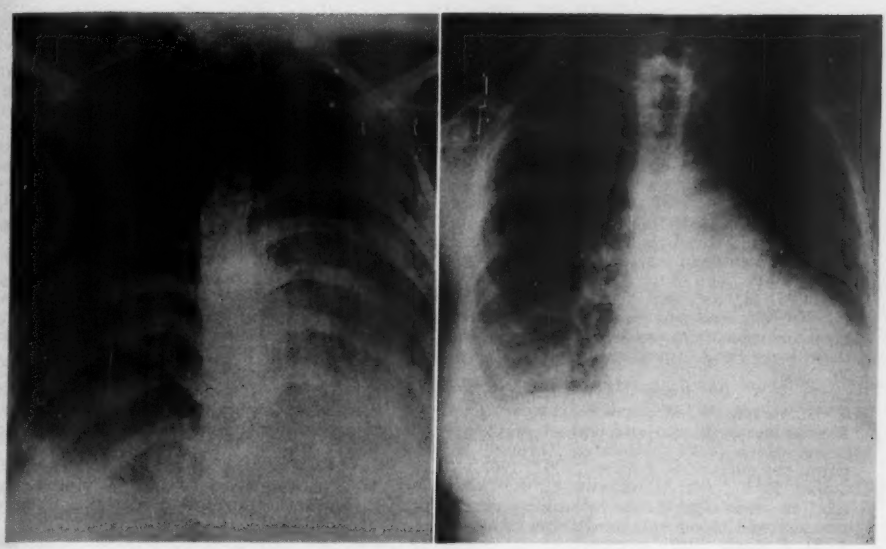

FIG. 4. Case 5. *A* (*left*). Bilateral scattered patchy densities typical of pulmonary insufficiency following bypass. *B* (*right*). Marked improvement three weeks after surgery.

Improvement was slow until the seventh postoperative day. The temperature returned to normal. Cyanosis disappeared, and respirations were no longer labored. Intermittent temperature elevations persisted for two weeks. The chest x-ray showed a gradual clearing over the same period (fig. 4*B*).

On September 3, 1958, a repeat right heart catheterization was performed. There was no evidence of left to right shunt. The patient was discharged from the hospital the following day.

Comment. The lungs were inflated intermittently with 100 per cent oxygen. Use of a 50 per cent helium-50 per cent oxygen mixture seems to be followed by a lower incidence of pulmonary complications.

SUMMARY

1. Special measures to cope with selected problems in postoperative care following cardiopulmonary bypass have been reviewed.

2. Central venous pressure determinations have aided in management of hypervolemia, hypovolemia and cardiac failure.

3. Hypothermia appeared therapeutically beneficial in a single patient with neurologic injury due to air embolism.

4. Sodium bicarbonate therapy is of aid in treating severe metabolic acidosis. Immediate refrigeration of donor blood reduces initial acidosis of oxygenator blood and, when combined with a high flow, normocapnial perfusion, virtually eliminates the problem of metabolic acidosis.

5. Transfusions are at times required to correct anemias resulting from reduced red cell survival time.

6. Tracheostomy, intermittent positive pressure breathing and steroids have been used in treatment of pulmonary complications.

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Dr. Robert S. Cartwright
Lovelace Clinic
4800 Gibson Blvd. S. E.
Albuquerque, New Mexico

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SOME UNUSUAL TUMORS OF THE STOMACH

CHARLES C. RUTLEDGE, M.D.*

Hazard, Kentucky

This is a report of 6 cases of what are considered unusual lesions of the stomach particularly with reference to diagnosis at the time of surgery.

The first case is a case of adenocarcinoma of the gall bladder with metastasis to the cystic nodes and the lower portion of the stomach with no obvious spread to other areas.

The usual spread of a carcinoma of the gall bladder is to the common bile duct or liver with metastasis along the lymphatics into the cystic lymph nodes and then the retroperitoneal lymph nodes, mediastinum and the lungs. Extension and perforation into the colon or duodenum also occurs.[1]

CASE 1

This 68-year-old white woman had a one-month history of intermittent nausea, cramping abdominal pain and anorexia with vomiting and inability to retain food for two weeks. She stated that she had had a similar episode with her first child 52 years ago.

Examination. A freely movable mass about 4 cm. in diameter was found about the level of the umbilicus.

Gastrointestinal series showed obstruction and narrowing of the gastric antrum and the pyloric canal.

At operation, there was an annular lesion at the pyloric end of the stomach approximately 3 in. in length and 1½ in. in diameter. This was hard and somewhat indurated; the remaining portion of the stomach did not seem to be affected. The gall bladder was very hard and somewhat indurated. The stomach and gall bladder were not in contact and were not adhered together in any way. There were enlarged lymph nodes in the gastrohepatic ligament and in the gastrocolic ligament. The pancreas was quite soft. The duodenum felt completely negative. The liver contained no nodules and there was no induration or thickening along the common duct. A subtotal gastric resection and cholecystectomy was done with tumor being obviously left in the liver bed.

The gall bladder contained seven stones.

Pathology report. Microscopic. Nearly the entire mucosa was replaced with a fairly high grade infiltrative adenocarcinoma that extended to the serosal coat. The tumor in the stomach was morphologically similar to the gall bladder primary. The mucosa of the stomach and duodenum showed no atypicality. The general impression was gained that the tumor in the stomach was growing in from the serosa rather than out from a primary site in the stomach. The tumor was diagnosed as a high grade infiltrative adenocarcinoma of the gall bladder with metastasis to the cystic nodes and lower portion of the stomach. There were 10 positive nodes out of 12 from the lesser curvature. There were 4 positive nodes out of 6 from the greater curvature.

The patient is now two months post operative and is doing well.

The second case is a leiomyosarcoma in a 9-year-old white boy. This is felt to be an exceedingly rare tumor particularly in a 9-year-old boy. At the Mayo Clinic from 1907 through 1946, there were 16 cases of leiomyosarcoma out of 10,000 cases of gastric carcinoma. In only two of these was the patient under 20 years of age. Their youngest patient was a boy 10 years of age.[2] This lesion comprises about 10 per cent of gastric sarcomas which in turn are found about 1 in 100 cases of carcinoma of the stomach; therefore, a leiomyosarcoma should be expected to occur about 1 for every 1000 cases of gastric carcinoma.

This is considered one of the less malignant of the tumors of the stomach.[3]

CASE 2

A 9-year-old white boy was admitted August 3, 1956, with a history of bleeding for three days with tarry stools. There had been no vomiting. Hemoglobin was 5.9 gm. He was given 500 cc. of whole blood and was discharged four days later with a hemoglobin of 9.45 gm. A gastrointestinal series was done on August 6 which was essentially negative. He was next seen October 16, two months later,

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* From the Hazard Clinic, Hazard, Kentucky.

with a hemoglobin of 6.9 gm. and a history of tarry stools. He was given 500 cc. of whole blood. The hemoglobin was brought up to 10.7 gm. and the patient was discharged 3 days later. He was next seen November 5 with a complaint of tarry stools. On this admission, he had an exploratory laparotomy with a pre-operative diagnosis of Meckel's diverticulum. A firm tumor was found on the lesser curvature of the stomach and a gastric resection was done.

Pathology report. Beneath the serosa in the lesser curvature of the stomach, there were several firm white nodules, the largest measuring 15 mm. in diameter. These were attached to a firm tumor which had largely replaced the stomach wall and protruded into the lumen of the stomach as a cauliflower lesion measuring 5 cm. in diameter. The tumor had an abrupt margin but did not show extensive infiltration in the wall of the stomach. The neoplasm extended to the pylorus but not into the duodenum. The rest of the gastric mucosa was essentially normal. Diagnosis was leiomyosarcoma of the stomach.

The patient was last re-evaluated December 1958, two years following operation, and was doing well with no recurrence of tarry stools.

The third case was a linitis plastica in a 30-year-old white woman with an accompanying carcinoid of the appendix.

Stout states that of the Presbyterian Hospital cases of carcinoma of the stomach 4.5 per cent were called linitis plastica or fibrous carcinoma.[4]

This condition occurs mostly between the ages of 40 and 70 and in the male two to one.[6]

CASE 3

This 30-year-old white woman had had epigastric pain and burning for three weeks before examination and had had some stomach trouble for six years.

A gastrointestinal series showed a fusiform narrowing at the junction of the antrum with the body. There was a small ulcer crater in this region.

At operation, the stomach was found to be thickened on the greater curvature from the pylorus proximally about 5 in. The remaining portion of the stomach was more thickened than normal but lessened proximally. There were no lymph nodes palpable.

Pathology report. This showed linitis plastica, no evidence of regional lymph node involvement and carcinoid of the distal tip of the appendix showing serosal extension.

The patient is doing well and slowly gaining weight 17 months postoperatively. She has spells of vomiting. A gastrointestinal series January 2, 1959, showed a normally functioning stoma following subtotal gastrectomy.

The fourth case is a giant benign ulcer of the stomach measuring 5 cm. in diameter in a 59-year-old white man.

Turner and associates[5] report 100 cases of benign gastric ulcers more than 4 cm. in diameter out of 2800 patients with gastric ulcer treated surgically (4.1 per cent). One of their cases had been operated previously and termed inoperable carcinoma and closed.

This case is presented because of the great likelihood of its being confused with a carcinoma. Our first reaction on examining the stomach was that it was a carcinoma which had spread into the pancreas and liver and was inoperable. This happened in one of the cases of Turner and Dockerty which had been operated previously and termed inoperable carcinoma and closed without resection.

CASE 4

History. The patient was admitted with a chief complaint of pain in the epigastrium with nausea and vomiting for three weeks. He had lost weight from 250 down to 177 lb. in two years but claimed this was due to dieting.

Past history. At the age of 19, he was treated for lues with eight or nine "shots" and had more treatment at the age of 39.

Gastrointestinal series showed a large filling defect along the lesser curvature of the stomach, just distal to the cardiac orifice and measuring approximately 7 x 6 cm. In the center of this defect, there was a negative shadow so that the whole configuration resembled a horse collar.

He was kept in the hospital for approximately one month due to electrocardiographic changes and then a high gastric resection was done. At operation, the stomach was found to be adherent to the under surface of the liver and the pancreas. The pancreas was very hard and indurated. There were no nodules in the liver and no nodes were palpated along the aorta or the gastrohepatic or gastrocolic ligament. The ulcer was approximately 2 to 2½ inches in diameter. It had eroded into the liver and into the pancreas.

The patient is doing well six months postoperatively.

The next case is that of phytobezoars of the stomach with associated gastric ulcer. This is a condition often mentioned but seldom actually

encountered. About 40 per cent of the cases of bezoars are phytobezoars, in other words, composed of vegetable fibers. Persimmon is responsible in about three-quarters of the cases and nearly 80 per cent occur in men.[6]

Most cases of trichobezoars or hairballs occur in women. A review of the literature in 1950 showed 400 recorded cases.[7]

CASE 5

This is a case of a 66-year-old white woman who had sudden severe abdominal pain on the day of hospital admission but had had pain and soreness and burning in the abdomen for about three and a half weeks previously. She had had "heart burn" for many years. A gastrointestinal series nine years ago showed an inactive ulcer.

She stated that she loved persimmons and had eaten them each week-end during the persimmon season last year, frequently eating 18 or 20 at a time and several times as many as 40. She stated she had not eaten them but one time this year.

Gastrointestinal series showed two masses within the stomach which were persistent and freely movable. There was a large ulcer crater on the lesser curvature of the stomach measuring 2 x 0.6 cm. The two masses were felt to be phytobezoars by the radiologist.

Operation revealed two hard phytobezoars, one 5 cm. and one 6 cm. in diameter. There was a gastric ulcer on the lesser curvature measuring 1½ by 2 cm. in diameter and approximately ½ cm. in depth. A sub-total gastric resection was done. The patient is doing well two months postoperatively.

Pathology report. This showed a large ulcer about 2 cm. in diameter, having a thick wall and a wide crater. There was a large bezoar about 5 cm. in diameter which on section showed a tan colored powdery material. Hair was not present.

The last case is presented to indicate that we do not always know how a cancer of the stomach is going to act. Sometimes we are mistaken on our prognosis. This was a 24-year-old white man who had a gastric resection for what was diagnosed as adenocarcinoma but later turned out to be a malignant lymphoma.

Lymphoid tumors vary from 0 to 4 per cent of all gastric malignancy. In a report of 7 cases of primary lymphosarcoma of the stomach reported from Touro Infirmary from 1942 to 1956, there was an incidence of 2.1 per cent. The prognosis is more favorable than that for carcinoma and treatment of choice is radical surgery followed by radiation.[8]

CASE 6

History. The patient had a history of "stomach trouble" for two years, with massive hemorrhage 1½ years previously and hospitalization six times for this trouble.

Gastrointestinal series showed a duodenal deformity but no ulcer crater. Gastric analysis showed no free hydrochloric acid. After histamine stimulation free HCl was 80°, total acidity 80°. At operation on May 2, 1951, a large gastric ulcer was found on the anterior surface near the lesser curvature in about the midportion of the stomach.

Pathology report. This showed grade four malignant neoplasm, probably adenocarcinoma with a large area of ulceration.

The patient was given 2400 r skin dose x-ray therapy to the tumor area.

Two years later, the patient had a tumor removed from the tonsilar fossa which was diagnosed as malignant lymphoma. On review of the previous slides, a pathologist felt that the gastric tumor must have been the same type of tumor. The patient was then given 2898 r skin dose x-ray therapy to the nasal pharynx and adjacent node drainage area.

Eight years later the patient is working regularly and doing well.

Hazard Clinic
Hazard, Kentucky

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CATARACT SURGERY

JAMES P. RIGG, M.D. AND ROBERT W. RIGG, M.D.

Grand Junction, Colorado

Ophthalmic surgery is delicate and refined, and it embodies three of the most necessary attributes of the surgeon which were laid down by Monihan approximately 20 years ago. These are: "The Lady's Hand, the Lion's Heart, and the Eagle's Eye." Cataract surgery naturally involves the various types of cataracts: congenital juvenile, nuclear, traumatic, mature, Morgagnian, *et cetera.*

INDICATIONS FOR CATARACT SURGERY

Many important considerations must be properly evaluated before cataract surgery is to be recommended. These are manifold and pertinent and they embody the following:

1. The reduction of useful vision in one or both eyes. If the patient has previously been examined before the cataract formation, and retinal and and macular changes have reduced the vision below 20/200, and subsequently a cataract forms, then the ophthalmic surgeon should be most cautious in recommending any surgery. There are exceptions to this rule; if the peripheral vision is good and a mature cataract has formed or if the central vision is less than 20/200, yet the peripheral vision is moderately good, one could justifiably recommend cataract surgery. These are individual cases and must be most carefully evaluated. With the above cases are borderline ones with 20/100 visual acuity or less.

2. If the vision of one eye has been reduced by a cataract formation to 20/100 or less, and the opposite eye shows no evidence of a cataract and the vision is 20/20 with a corrected lens, one again should be cautious about recommending cataract extraction of the one affected eye especially if the patient is beyond 55 or 60 years of age. In younger individuals it is to be recommended to make the extraction of the cataract and follow this with a corneal (contact) lens at the surgeon's discretion. If, however, the patient is in the fifth or sixth or later decade of life and there is definitely evidence of a cataract forming in the opposite eye although the vision is still moderately good, one is justified in recommending that cataract of the one eye—the one which has less than 20/100 visual acuity—should be operated. Remember that hypermature cataracts are extremely difficult to operate, and the hazard in conjunction therewith is far greater than in an immature cataract.

3. Naturally also in this discussion, if with one eye the patient can read quite well and has approximately 20/20 visual acuity and is in the older age group, the surgeon has to advise cautiously on removal of the cataract from the opposite affected eye.

4. If the visual acuity has been reduced in one eye to less than 20/100 and in the other eye to 20/50 or less, it certainly is advisable to recommend that surgery be performed on the eye that has the greater reduced vision.

5. If one eye has previously been operated and is an aphakic eye, and the other eye shows definite manifestations of nuclear sclerosis and peripheral cortical changes and the vision has been reduced to 20/70 or less, or even possibly in some cases to 20/50 or less, then it is justifiable to recommend that surgery be performed on the second eye before the cataract is mature. The differential in an aphakic eye with a large plus correction over an eye with perhaps a slightly minus correction causes aberration of objects and oftentimes diplopia, and usually when the second eye is operated there is binocular single vision. Although sometimes a small component of prism may have to be incorporated in the refraction it is justifiable in these cases, as mentioned above, to recommend that the surgery be performed a little earlier than one would ordinarily recommend.

6. Occasionally patients are extremely apprehensive when the threshold of visual acuity has been reduced in one eye, and subsequently in the opposite eye, and there is upon examination definite evidence of cataract formation. Then for the mental benefit of the patient, and justifiably so, in order to improve the visual acuity if it has been reduced in both eyes to less than 20/50 or 20/60, and we can anticipate the possibility of

20/30 to 20/20 visual acuity, we should definitely recommend cataract extraction.

7. It must be remembered that early cataract extraction in cases where vision is being lowered bilaterally is most advisable, and, as previously mentioned, hypermature cataracts are much more difficult to extract, and that the longer a patient does not see with an eye the greater the possibility of a poor result, because macular changes may occur due to nonuse.

8. One-eyed patients are always a problem, and the dexterity of the surgeon, the history, the health, and the mental attitude of the patient, and the careful analysis as to what has caused the loss of the opposite eye must be taken into consideration, and each individual case carefully screened before surgery is recommended.

9. Cataract surgery on both eyes at the same time has been discussed by ophthalmic surgeons for many, many decades. We have operated a few score of such types of individuals (*i.e.*, operating both eyes concomitantly), but in the over-all picture not too great a number. We operate one eye and then change everything from the operative standpoint and perform surgery on the opposite eye. This has advantages because many patients would prefer to have only one operating room visit. The preoperative orders are for only one time, the transferring from the room to the operating room is only once, the meeting of the strange faces in the room are for only one time, so there are some indications for this procedure. Yet we do it very rarely. If both eyes are to be operated, we prefer to have a lapse of two to four days from one eye to the other, although the cases where we have operated both eyes at the same sitting have been most excellent. Even if both eyes are bandaged the patient is forewarned with reference to this and the results have been most gratifying.

10. The presence of glaucoma is always a problem, but it is my opinion that every glaucoma case that has a cataract should be operated. The intumescent lens certainly bulges forward the iris, and the iris angle is blocked, glaucoma is enhanced, vision is diminished, and the hazard of operating such a case is not too much greater under modern treatment than the case that does not have glaucoma. The fact that this large lens is removed is beneficial to the glaucomatous state of the eye and in all of these cases, of course, one, two or three peripheral iridectomies should and must be performed.

11. Inflammatory processes of the eye and cataract surgery is a question open to discussion and in low-grade cases of uveitis one can foresee that any intraocular surgery could be condemned. By the same token the patient does not see adequately and the low-grade inflammatory process can usually be controlled by medical therapy, systemically and topically.

INTRACAPSULAR VERSUS EXTRACAPSULAR EXTRACTION

Occasionally it may be justified to recommend extracapsular extraction or splitting of the capsule of the lens and extraction of the cortex, although this is becoming more and more a rarity. Intracapsular extraction should be recommended in every case where it is possible. Even in juvenile and congenital cataracts intracapsular extraction can be performed and has been done expeditiously. Naturally there are hazards connected with all types of cataract surgery, but by and large intracapsular cataract extraction is to be condoned and not to be condemned; the exceptions are few and far between. The possibility of iris prolapse and of vitreous loss is, to be sure, greater in intracapsular extraction than in extracapsular extraction, but the results from the refined method of intracapsular extraction far exceed the hazard of iris prolapse and/or vitreous loss. There is no question that a fluid vitreous is possibly the contraindication to intracapsular cataract extraction. Although small amount of fluid vitreous is lost, it may reduce the visual acuity. Subsequently, the visual acuity is usually far better than the result obtained by doing an extracapsular extraction.

PREPARATION OF THE PATIENT

After a cataract has been diagnosed (macular perception, peripheral perception, tonometric reading, biomicroscopy, ophthalmoscopic findings, and other refined determinations) a complete family and individual history and a complete physical examination including laboratory and bacteriologic study are obligatory. An evaluation of the paranasal sinuses, the teeth, even the abdomen, pelvis in female patients, the prostate in male patients, and the nasolacrimal apparatus should be made. The clearing of foci of infection, especially the extraction of "snags"

of teeth, is highly to be recommended. A chronic sinusitis can be detrimental to good cataract surgery.

The mental status of the patient cannot be minimized. This considers the psychology of the patient, the need for adequate sedation to relieve where we have operated both eyes at the same apprehension both before, during and after operation. I admire my ophthalmic surgeon colleagues who sit and talk with their cataract patients and give the patient the utmost reassurance. This is a great asset to the cataract surgeon. This reassurance instills confidence in the patient, and when the patient has confidence the results of the surgical procedure will be definitely greater than in the profoundly apprehensive, highly excited, nonconfident, and oftentimes semibelligerent patient.

The patient should be interrogated with reference to allergies and adverse reaction to any type of medication. After this, illustrations, discussions, even the showing of operated patients should all be disclosed. The patient should also be given information with reference to the fact that he or she is going to wear a thicker lens on this eye, but these subjects must not be delved into too deeply for fear of producing unwarranted apprehension on the part of the patient. One also discusses the pain, the type of anesthesia, the bandaging of the eye, the ambulation, the length of time in the hospital and, of course, the financial question. This gives these patients, even though they are elderly, well rounded disclosure as to what the surgeon is to do, and what the patient is to expect.

Medical preparation. Each surgeon has his own choice of preoperative medication. We prefer to operate in the morning and prefer to have the patient visit the office before hospitalization the afternoon before. We then see the patient at the hospital that evening, and even have the nurse in charge talk considerately to the patient, and reassure him that the surgeon has many such cases and that nearly all of them (even fudging a little) get along exceptionally well. The nurse at the office also has been instructed to do the same. All of these are little courtesies which we owe to our patients.

Nembutal or Seconal, 1½ gr., is given at 8:00 p.m. (the surgery is to be performed at 7:30 the next morning). Nembutal or Seconal, 3 gr., is given at 5:00 a.m. At 6:30 a.m. (depending on the age of the patient in all of these) the patient is given 50 to 100 mg. of Demerol and $\frac{1}{150}$ gr. atropine. Two tablets of Diamox, 250 mg., are given when the patient enters the hospital and repeated at 7:00 p.m. The age, the size, the general health, the blood pressure, *et cetera*, have to be taken into consideration, and each patient is preoperatively medicated according to these findings.

Anesthesia. Atkinson has made great contributions to the akinesia in ophthalmic surgery. Routinely we do both an O'Brien and Van Lint akinesia together with a retrobulbar akinesia. It is imperative to have digital pressure on the eyes as propounded by Atkinson and Chandler, and my good friend Paul Chandler states: "Have pressure on the eye for ten minutes after the infiltration of the local anesthesia." This reduces the pressure of the eye and if there is any indication of glaucoma or for greater pressure this is definitely reduced by digital pressure. Reduction of intraocular pressure certainly definitely reduces the possibility of vitreous loss, of intraocular hemorrhage, of iris prolapse, and of other complications.

Thorazine has been recommended both pre- and postoperatively as have other tranquilizers. Trilafon is a definite good adjunct. Even antihistamines oftentimes have a side reaction of tranquilization which is good for the patient. Postoperatively, Compazine, Thorazine, Trilafon, and many others can be recommended if there is any nausea. Sometimes these preparations given before surgery are to be recommended, at the surgeon's discretion.

The eye area, including the brow, is washed with soap and water (septisol, hexachlorophene 0.75 per cent). The eyebrow is not shaved, the eyelashes are not trimmed. Neosporin ophthalmic drops and sodium sulamyd drops are instilled in the eye. The pupil is dilated with Neosynephrine 10 per cent before transference to the operating room.

METHOD OF EXTRACTION

Previously we have mentioned that as many intracapsular surgical extractions should be made as possible regardless of the type of cataract. There are those who advocate conjunctival flaps and more and more ophthalmic surgeons do their cataract extractions with a conjunctival flap. Many thousands of excellent intracapsular ex-

tractions have been made without the conjunctival flap. Preplaced corneal-scleral sutures are to be recommended. It is very difficult to put sutures through an incision at the limbus when the eye is soft; it is difficult to pick up the iris, and to get adequate sutures placed without damaging the eye. In the hands of some expert surgeons this is performed. We certainly recommend a preplaced suture, whether one uses a conjunctival flap or not. If a flap is made and laid down and then the sutures placed, the number of sutures depends on each individual surgeon. The more sutures you have, if they are preplaced, the greater number of tiny threads you have to sort out in order eventually to get at the lens which is the cataract. Three sutures, one each at 10, 12, and 2 o'clock are usually sufficient, although there are some very great men who place five to seven sutures. The type of suture material varies again with each individual, although the 6-0 black silk through the Grieshaber needles certainly is a beautiful type of suture to use, and we can highly recommend it. Chandler threads through these sutures and cuts through them with a von Graefe knife when he makes his incision and then puts in 6-0 chromic absorbable sutures. He does a beautiful cataract extraction.

Type of incision. The instrument of choice in our hands is the keratome. After the keratome incision has been made this is enlarged with a Steven's scissors or a Castroviejo scissors. Rarely do we cut a preplaced suture, but occasionally this hazard is encountered. The incision should approximate 180°.

The reason for the keratome incision is that in the hands of most of us it it easier to do than the von Graefe incision with the puncture and counter puncture. The enlargement of the keratome incision is not a difficult procedure. Of course, you may have a few occasionally small ragged edges, but most of the time these are insignificant or even are not present.

Extraction of the lens. More and more surgeons are attempting to use the erisophake* and undoubtedly within the next decade all younger trained ophthalmologists will use the erisophake and it only. In our experience we think it is excellent, and most lens can be extracted with the erisophake by placing it on the lens and, with the suction apparatus, lifting and gently tugging and sliding until the lens is lifted from the face of the vitreous. The Verhoeff forceps as an adjunct to the erisophake is to be recommended and we have removed many hundreds of cataracts by retracting the iris after a peripheral iridectomy has been performed; be sure to do either one or two peripheral iridectomies near the base of the iris in nearly all cases. This still leaves a round pupil and it is to be recommended. Now progressing after retracting the iris, reach down at the upper end of the capsule of the lens, and pick up and lift the lens out of its bed.

It is necessary at times to do a complete iridectomy, and occasionally the lens has very tough zonular fibers or is attached to the face of the vitreous and the vitreous can be pulled out with the lens. This, of course, is extremely rare but it does occur. By sliding the lens around gently when you are lifting it out either with the erisophake or the forceps, you will find that it will usually come out with a moderate degree of ease. Be gentle in all these procedures and have the assistant retract or lift up the cornea so that you have adequate visualization of the lens.

After the lens is extracted, the sutures are tied. The iris may have to be reposited—we hope there will have been no vitreous loss. The flap is sutured with 6-0 chromic or plain catgut if a conjunctival flap has been made. The round pupil is to be hoped for, and in most cases can be obtained.

CARE OF THE PATIENT

Medication used at the time of the bandaging. We always use neosporin ophthalmic solution in the eye, and one of the antibiotic or sulfonamide drops or ointments. If the pupil is small, dilate the pupil, if the pupil is large do not put in a mydriatic. These medications are instilled at the time of the dressings.

If one eye is operated bandage only one eye. A binocular black shield over the eyes with holes cut in to look through certainly is of merit, although one can just bandage one eye and urge the patient to keep both eyes closed most of the time and remain moderately quiet during the first 24 hours. A little turning is not to be condemned, and we have even had patients out of

* Since the preparation of this manuscript we have performed 160 cataract extractions with the use of the erisophake only, and the results have been extraordinarily excellent. We highly recommend it.

bed 6 hours after the surgery, but to me there is still the possibility of a retinal or choroidal separation because of a little pressure on the wound. The elderly patient is sometimes confused and does not cerebrate quite as well as he might, and disorientation is not good. After 24 hours, or sooner sometimes, the patient is given bathroom privileges. The operated eye is kept bandaged with daily dressings. The patient may sit up for a period of time, may walk around on the third or fourth day and oftentimes leaves the hospital on the fifth day, but we prefer to keep most of them for 6 to 8 days depending on the patient's attitude and progress.

Antibiotics are given almost routinely both pre- and postoperatively, and steroids are given in most cases both systemically and oftentimes topically. Up to the present time we have seen no deleterious results therefrom. Confidence and reassurance are still good aftercare thoughts.

The sutures are removed in approximately 10 days, sometimes 2 weeks, sometimes even as early as 7 days, and we have left them in for a period of 2½ to 3 weeks.

A good refraction is not possible under 3 to 5 weeks, and preferably 6 to 8 weeks. There certainly may be changes in the refractive error up to 2 or 3 months so that one must tell the patient if it is under 4 or 5 weeks that there may be some change within the next few months.

CATARACT SURGERY COMPLICATIONS

This alone is a subject for a paper and one could discuss it almost *ad infinitum*. Some complications are: (a) iris prolapse; (b) vitreous loss; (c) retinal detachment; (d) choroidal separation; (e) anterior chamber hemorrhage; (f) vitreous hemorrhage; (g) pupillary block; (h) pupillary membrane formation; (i) vitreous degeneration; (j) hypotony; (k) glaucoma; (l) wound leak; (m) failure of wound to close; (n) drug sensitivities; (o) psychosis; (p) cardiovascular-renal involvement; (q) gastrointestinal disorders; (r) bacterial infection of eye, uveitis, panophthalmitis; (s) hammock-shaped pupil.

CORNEAL (CONTACT) LENSES IN APHAKIC EYES

These may be tolerated and worn in the younger age groups quite advantageously. In cases of younger individuals where one eye has developed a cataract due to trauma, then a corneal (contact) lens is advised and usually worn admirably.

In senile cataract cases (aphakic) the average patient will neither tolerate nor be adept at inserting the small corneal lens. Each case is individually evaluated.

Dr. Robert W. Rigg
Rigg Bldg.
Grand Junction, Colorado

A RATIONAL APPROACH TO THE THYROID MALIGNANCY PROBLEM*

HENRY GOODWIN GLASS, M.D., GEORGE W. WALDRON, M.D.,
HERBERT C. ALLEN, JR., M.D., AND
WILSON G. BROWN, M.D

Houston, Texas

The major factors that lead to the variance of opinions in reference to thyroid cancer stem from a lack of agreement on the incidence, diagnosis, and treatment of the disease. In spite of this disagreement a rational approach to the management of thyroid malignancy can be reached.

For the first 30 years of operation of the Hermann Hospital in Houston, Texas, there were 252,224 patients admitted. From this group, 1,409 or 0.6 per cent patients underwent thyroidectomy. There were 724 patients with nontoxic nodular goiter of which 110 or 15.2 per cent were malignant, 366 patients with toxic diffuse goiter of which 10 or 2.7 per cent were malignant, 186 patients with chronic thyroiditis of which 9 or 4.8 per cent were malignant, 101 patients with toxic nodular goiter of which 8 or 7.9 per cent were malignant, and 28 patients with a nontoxic diffuse goiter or diffuse colloid goiter of which 4 or 14.3 per cent were malignant. The subdivisions and percentages in these groups are shown in table 1.

The three metastatic squamous cell carcinomas were from the oropharynx and the tongue. The primary site of the metastatic melanoma was not identified. The primary complaint and the reason for thyroid surgery in these four cases was the presence of a nodule in the thyroid area.

Comparative studies concerning the incidence of malignancies coexistent with other thyroid diseases are shown in table 2.

The reason for the variance in percentages of thyroid malignancies in different sections of the country is not clearly understood, but geographic location seems to have an influence. It might also be on the basis of total number of cases studied and whether or not the series were consecutive. The reason for the high incidence in this study is not known but is under further investigation.

* From the Departments of Surgery, Radioisotope Medicine, and Pathology, Hermann Hospital, Houston, Texas.

TABLE 1

Types of goiter

Type	Benign	Malignant	Total	Per Cent Malignant
Nontoxic nodular				
Single nodule	312	39	351	11.1
Multiple nodules	302	71	373	19.0
	614	110	724	15.2
Nontoxic diffuse	24	4	28	14.3
Toxic diffuse	356	10	366	2.7
Toxic nodular				
Single nodule	45	1	46	2.2
Multiple nodules	48	7	55	12.7
Chronic thyroiditis				
Reidel's struma	13	1	14	7.1
Nonspecific thyroiditis	33	1	34	3.0
Hashimoto's Disease	130	7	137	5.1
Tuberculous thyroiditis	1	0	1	0
Metastatic squamous carcinoma		3	3	
Metastatic melanoma		1	1	
Totals	1264	145	1409	10.3

PATHOLOGIC DATA

The following criteria used to establish a diagnosis of malignant disease of the thyroid gland have been almost universally accepted. The gross as well as the microscopic appearance of the gland is important.

1. The presence of thyroid tissue which may be either well or poorly differentiated but which is found extrinsic to the gland capsule or within one or more lymph nodes of the neck.

2. Gross or microscopic invasion of blood vessels.

3. In the case of an encapsulated adenoma, penetration through the capsule.

4. The presence of papillary growth, supported by cell atypism.

TABLE 2

Comparative studies of thyroid malignancy in other areas

Investigator	Malignancy	Investigator	Malignancy
	per cent		*per cent*
Horn *et al.*, Philadelphia		Cattell and Colcock, Boston	
All nodular goiters	5.5	All nontoxic nodular	10.2
All goiters	3.0	All toxic nodular	1.8
		All nodular goiters	9.1
Stubenbord *et al.*, Buffalo		Pemberton *et al.*, Rochester	
All nontoxic nodular	7.0	Nontoxic nodular	7.5
All nodular goiters	2.8	All nodular goiters	4.8
All single nodules	3.1	Toxic nodular	<1.0
All goiters	2.1	Exophthalmic goiters	0.5
Cole *et al.*, Chicago		Crile, Cleveland	
Nontoxic nodular goiters	17.1	Nontoxic nodular	10.9
Nontoxic single nodule	24.4	Nontoxic, single nodule	24.5
All nodular goiters	8.0	All nodular goiters	5.6
Dailey *et al.*, San Francisco		Ross, Los Angeles	
All single nodules	15.6	All thyroid surgery	4.0
All goiters	4.8		

5. In the absence of all of the previous findings the diagnosis of malignancy is seldom, if ever, made, although in rare instances the actual appearance of epithelial cells is adequate to support a diagnosis of malignancy. Such changes must include nuclear enlargement and extreme hyperchromatism, abundant mitoses, some atypical and often bizarre multinucleated cells.

CLINICAL DATA

The clinical histories of the 145 patients with thyroid cancer revealed that 107 or 73.8 per cent were female, 38 or 26.2 per cent were male, 126 or 86.9 per cent were white, and 19 or 13.1 per cent were Negro patients. The age distribution showed the greatest number of thyroid cancers in the third, fourth, and fifth decades (table 3).

TABLE 3

Age and sex distribution of patients

Age	Female	Male	Total
years			
1–10	1	0	1
10–20	8	4	12
20–30	25	4	29
30–40	22	6	28
40–50	20	11	31
50–60	10	4	14
60–70	13	2	15
70–80	7	6	13
80–90	1	1	2
Totals	107	38	145

It is important to note that while 90 or 62 per cent of the patients complained of lumps in their throats, 20 or 13.8 per cent of the nodules were found on routine physical examination. The other 35 or 24.2 per cent had no palpable nodules (table 4).

Duration of symptoms (table 5) had no consistent pattern, ranging from 1 month to 33 years.

TREATMENT

Preoperative treatment was given to 24 patients. The varying types of treatment are due to the fact that different surgeons were treating the patients independently (table 6).

The surgery performed on these 145 patients with carcinoma is shown in table 7. It should be emphasized again that the reasons for the different types of treatment are due to the multiplicity of operators, the long period the study covers, the changing surgical trends during that period, and the fact that some of the patients refused surgery until late in the disease process (table 7).

From the study of the treatment of 145 patients with thyroid malignancy shown in the preceding tables, certain conclusions and recommendations are offered.

1. A total thyroidectomy is recommended for all multiple toxic and nontoxic nodular goiters. On the basis of malignancy percentages alone, this recommendation is justified. Recurrence of toxicity and hyperplasia of the remaining tissue likewise speak for this form of surgical therapy. Recurrent nontoxic nodular goiter is not uncommon, nor is occult carcinoma in the nodular mass left when subtotal thyroidectomy is performed. Of major importance in the reasons for doing a total thyroidectomy is the removal of all the thyroid tissue present in the gland area. This aids immeasurably in the postoperative pickup of radioactive iodine by the metastatic tissue when postoperative studies are done.

TABLE 4

Major presenting symptoms of patients

Symptom	Number of Patients
Mass or swelling in the neck	90
None: found on routine examination	20
Choking or difficulty in swallowing	10
Hyperthyroidism	13
Dyspnea	5
Nervousness, without signs of hyperthyroidism	5
Hypothyroidism	2
Totals	145

TABLE 5

Duration of symptoms of patients

Duration	Number of Patients
1 to 6 months	14
6 months to 1 year	8
1 to 2 years	15
2 to 3 years	5
3 to 4 years	9
4 to 5 years	4
5 to 10 years	13
10 to 15 years	6
15 to 20 years	4
20 to 30 years	1
33 years	1
Found on routine physical examination	20
Patients did not know duration	45
Total patients	145

TABLE 6

Preoperative treatments given

Type	Number of Patients
Preoperative irradiation	14
Preoperative radioactive iodine	8
Preoperative x-ray and radioactive iodine	1
Radium implantation	1
Total patients	24

TABLE 7

Types of surgery performed

Surgery	Number of Patients
Total thyroidectomy	75
Lobectomy	18
Subtotal thyroidectomy	15
Hemithyroidectomy	12
Partial lobectomy	7
Total lobectomy and subtotal opposite lobe	6
Excision of tumor	6
Biopsy of tumor	6
Total patients	145
Additional surgery performed at time of original surgery and combined with one of the above, or after one of the above	
Unilateral radical neck dissection	47
Bilateral neck dissection	7
Modified neck dissection	2
Total patients	56

Endogenous or exogenous thyroid stimulating hormone will stimulate metastatic thyroid masses better after all normal glandular tissue from the thyroid area has been removed. As long as there is any normal functioning thyroid tissue remaining, there is less likelihood for abnormal thyroid tissue, which has previously failed to concentrate radioactive iodine, to begin to function or concentrate radioactive iodine. It is believed that this is a competitive phenomenon for the thyroid stimulating hormone.

2. If surgery is to be done a total thyroidectomy is recommended in nontoxic diffuse

goiters, 14.3 per cent of which are malignant in this survey. This excludes that group of adolescent colloid goiters which are occasionally treated by subtotal thyroidectomy. A total removal is not desirable in these cases because of the hazard of growth disturbance.

3. A total thyroidectomy is recommended for all forms of chronic thyroiditis in its later stages on the basis of the usual generalized involvement of the gland coexistent with hypofunction, some euthyroidism or hyperfunction in the earlier stages. The gland is usually nodular, hard, and there is no clear line of gross demarcation between normal and abnormal tissue. Multiple small adenomas or diffuse nodular thyroiditis cannot be distinguished grossly at the operating table. A subtotal thyroidectomy or lesser procedure for chronic thyroiditis is not rational when the majority of these patients are hypothyroid before surgery, the nodules cannot be felt or distinguished from inflammatory tissue, and there is a high incidence of malignancy coexistent in the disease. The use of needle biopsy, removal of the thyroid isthmus or other minor procedures for the treatment of chronic thyroiditis is not recommended. A needle biopsy may miss multicentric areas of malignancy, and relief of compression is not a reasonable method of treating cancer, if it is present.

4. A total thyroid lobectomy is indicated in all single nodules. This includes removal of the isthmus and pyramidal lobe as a principle of total lobectomy. The anterior portion of the opposite lobe is also excised for diagnostic and cosmetic purposes. If a malignancy is found, a total thyroidectomy is done, and the principles of surgical therapy as outlined below then apply.

After a total thyroidectomy has been done because of the presence of malignancy found on frozen section, the neck is searched for gross metastasis. Recently, a specially designed surgical scintillating probe has been devised to scan the operative, adjacent, and mediastinal areas for obscure functioning metastases, provided a preoperative dose of radioactive iodine has been given. If metastasis is found a radical neck dissection is done on that side. If bilateral metastases are identified a radical neck dissection is done on the side of major involvement. Later a modified neck dissection may be done on the second side leaving the jugular vein.

As soon as possible after total thyroidectomy for carcinoma of the thyroid an uptake and gammagram study is done to see if there is residual functioning thyroid tissue. This holds true whether or not a radical neck dissection has been done. If no functioning thyroid tissue is found by the immediate postoperative gammagram the patient is allowed to go 6 to 8 weeks without supplemental exogenous thyroid therapy. By that time marked myxedema should develop unless a fair amount of functioning thyroid tissue is present. Varying with age, the patient is then given 5 to 10 units of thyroid-stimulating hormone daily for 7 to 10 days. The presence of residual functioning thyroid cells is then searched for by I^{131} uptake and gammagram studies. The thyroid stimulating hormone therapy is continued throughout these tests. If functioning thyroid tissue is found on gammagraphic study immediately after surgery, the time interval for specific radioactive ablation therapy is reduced to three to four weeks postoperatively.

No matter what the uptake values are, and they are a rough screening test to determine the residual tissue in the neck, gammagrams for specific localization in the lower head, neck and chest are done. For the detection of distant functioning metastases, the urine is collected for 48 hours and a radioassay made of the activity present. The percentage of radioactive iodine present in this 48-hour specimen plus the activity present in the cervical region should equal approximately 85 per cent of the orally ingested radioactive iodine. Failure to meet these criteria would indicate presence of distant metastases. If metastasis or metastases are found and radioactive therapy has been decided upon, 300 to 350 mc. of radioactive iodine are given in a single dose orally for adults. Generally 150 mc. are given to children. Thyroid-stimulating hormone is continued through the uptake, gammagram, and until 48 hours after the therapeutic dose of radioactive iodine has been given. Using the therapy as outlined, there is no definite way to determine what percentage of the metastatic carcinomas can be stimulated, for if the tumor is not stimulated and no mass is felt, only time will determine if such tumors can or cannot be stimulated either by endogenous or exogenous thyroid stimulating hormone. The long term followup on patients treated with this method will be the test of the value of the treatment.

The number of thyroid-stimulating hormone (TSH) and therapeutic radioactive iodine regimens required by a given patient depends upon the extent of the metastasis and the biologic behavior of the tumor. Of all the patients stimulated and treated by this method none have died. Some of the patients had diffuse and localized pulmonary metastases. Some have required four complete courses of thyroid stimulating hormone and radioactive therapy. Large pulmonary and cervical metastases have been ablated, at least according to clinical uptake and gammagraphic proof. In general, it takes no more than three therapeutic doses of radioactive iodine to ablate the metastatic disease. This is based on treatment of 25 to 30 new cases of carcinoma of the thyroid a year by this method. There have been no deaths from nonfunctioning (no pickup) metastatic carcinoma of the thyroid. Of 200 cases of carcinomas of the thyroid, 197 have no visible, palpable, or radioisotopic evidence of tumor to date. Three still have palpable and visible masses in the neck but have failed to concentrate I^{131} following large stimulating doses of TSH. These may represent primary thyroid cancer incapable of responding to TSH, but it is also possible that these tumors represent metastatic tumors from distant organs, *i.e.*, kidney, colon, ovary, breast.

There has been some discussion as to the rationale of stimulating carcinoma to pick up radioactive iodine and then ablating with radioactive iodine therapeutically. The end result thus far certainly justifies the means by which these masses are ablated, and for this reason, this regimen is being used. It is theorized that "cross-fire" technique is employed with this regimen, for the well functioning cells in the normal or abnormal thyroid tissue are stimulated suddenly and heavily to pick up radioactive iodine. Upon this sudden pickup of radioactive iodine, the functioning cells concentrate I^{131} and thus destroy themselves as well as the contiguous carcinomatous thyroid cells which fail to pick up the radioactive iodine. The percentage of patients who have had known exacerbations of disease has been small. It is known that the pituitary produces excessive amounts of thyroid stimulating hormone (endogenous TSH) after thyroidectomy, so the danger from exogenous stimulation for the periods outlined in this course of treatment is not considered important and is definitely clinically insignificant. The radioactive iodine treatment itself is probably in no way dangerous either, for there have been no cases of anaphylactoid rection or leukemia reported in any of the patients. There have been a few angioneurotic edema reactions to the thyroid stimulating hormone therapy, but these were easily treated, and there were no subsequent complications.

Some investigators believe that capsular breakdown is necessary for the diagnosis of thyroid carcinoma, but it is felt that this necessitates serial sectioning of all thyroid tumors, which is not practical, especially with the use of frozen sections. The criteria for diagnosis discussed previously in this paper form the basis for determining the presence of malignancy in this study. It is further noted that there is not true capsule in the occult sclerosing carcinoma of the thyroid gland.

The percentage of nerve injuries in this series is zero, and the amount of temporary hypoparathyroidism is not significant.

SUMMARY

Thyroid cancer is more prevalent in this series than most others. Geographic location, the consecutive nature of the series, and the pathologic classification might be responsible for the variance of these statistics with those found in the literature.

During a 30-year period, over 10 per cent of all thyroid glands removed surgically, for any reason, possessed coexistent primary thyroid cancer. Clinical data were significant in that 13.8 per cent of the thyroid cancers were found on routine physical examination.

It is not believed that any type of primary thyroid malignancy is innocuous. Total thyroidectomy and I^{131} studies with ablation of any residual functioning thyroid cells, according to the method described, is an important step forward in the handling of this disease.

Dr. Henry Goodwin Glass
1033 Hermann Professional Bldg.
Texas Medical Center
Houston 25, Texas

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THE ENDOCRINOLOGIC TREATMENT OF ADVANCED BREAST CANCER

ROBERT A. HUSEBY, M.D.*

Denver, Colorado

Data have been presented from several clinics, strongly suggesting that hormonal therapies for disseminated breast cancer, when successful, not only result in relief of pain and healing of clinically demonstrable cancerous deposits but also significantly prolong the life of the patient. It seems important, therefore, that every effort should be made to determine on the basis of the information presently available what the most rewarding approach to hormonal therapy might be under a number of different circumstances so that each patient might receive the maximal opportunity of benefiting from this type of palliative therapy. In such a consideration, we need to know the probabilities of success of the various types of therapy in patients of different age groups, with various anatomical distribution of lesions and with various antecedent responses to therapy. Although there are as yet many gaps in our knowledge in this regard, enough data are becoming available to begin to make meaningful correlations. However, because there are a number of factors that influence the response of metastatic breast cancer to endocrine alterations, several permutations and combinations must be considered. The situation is further complicated by the fact that subjective as well as objective considerations are of importance when evaluating the palliative effectiveness of any procedure.

GENERAL PRINCIPLES

Before considering specific details, there are a few general principles of therapy that seem to warrant emphasis. Since breast cancer characteristically metastasizes widely, it seems imperative that we assess the situation existing in every patient rather throughly before embarking upon any palliative procedure, be it radiologic or endocrinologic in nature. The decision as to what therapeutic regimen should be followed is then based on which of the demonstrable lesions offer the greatest threat to the patient's life and well being and which modality of therapy is most likely to bring about improvement in these most grave lesions. Thus, when major weight bearing areas of the bony skeleton are involved with significant metastatic deposits resulting in pain and a real danger of pathologic fracture, we feel strongly that, when feasible, x-ray therapy should be administered to these areas even though in addition we may wish to carry out some form of hormonal therapy in an attempt to control the less threatening disease in other parts of the body.

It should also be emphasized that with the additive types of hormone therapy the dosage levels that have been shown to be most effective are well above those thought of as representing the normal physiologic range. Although careful dose-tumor-response titrations have not been carried out, it is fairly definite, for instance, that when using an androgen, doses comparable to testosterone propionate, 50 to 100 mg. injected intramuscularly 3 times per week, or to fluoxymesterone, 20 to 30 mg. per day orally, should be employed. Such doses routinely result in varying degrees of masculinization, but to reduce the medication at the first sign of significant hirsutism, voice change, or alteration of complexion, by and large, is to assure defeat as far as any improvement of the patient's disease is concerned. Similarly with estrogen administration, dosages comparable to 15 mg. of stilbestrol or 2 to 3 mg. of ethinyl estradiol daily by mouth should be employed in spite of the fact that at such levels varying degrees of nausea and malaise, which are most usually transient, may be encountered during the first several days of therapy. When sufficiently severe, these symptoms usually can be alleviated by the concurrent use of the phenothiazine derivatives during the first two weeks of treatment or by substituting an injectable estrogen such as estrodiol benzoate 5 mg. 3 times per week for the period of initiation of therapy.

Finally, it is essential to follow the metastatic

* From the Department of Surgery, University of Colorado School of Medicine and the Bonfils Tumor Clinic, Colorado General Hospital, Denver, Colorado.

deposits carefully recording actual measurements of lesions wherever possible, for it is the experience generally that when definite progression of disease occurs in the face of continued therapy, nothing is to be gained by persisting with that particular therapeutic regimen. In fact, at times discontinuance of an administered hormone is followed by a definite improvement in the patient's disease. Such "regressions of withdrawal" most often occur in instances in which the patient first experienced improvement of her disease with the institution of therapy, but

FIG. 1*A*. Roentgenograms of a 66-year-old woman whose only demonstrable metastases were in her skeleton (the roentgenogram shows the early lesions in the pelvis). She was treated with testosterone propionate 100 mg. i.m. 3 times a week for 4 months before unequivocal evidence of progression of the disease was obtained.

FIG. 1*B*, the lesions were primarily lytic in character but with a few areas of blastic reaction. At this time the androgen was discontinued and no other therapy instituted.

FIG. 1*C*. During the next 3 months a moderate "alkaline phosphatase flare" was noted, multitudinous lytic areas throughout the skeleton calcified as shown in *C*, and the patient experienced a striking clinical improvement. During the past 3 months no evident change has occurred; the areas of calcification have not increased in size, as far as we can tell no new lesions have appeared and the clinical improvement has been maintained. It seems most probable that this case represents an incidence of "withdrawal regression" without an initial improvement and that the patient's condition had been made worse by the testosterone treatment. The skeletal lesions remained unchanged for an additional 6 months before areas of lysis began to appear. (This patient was treated at the American Medical Center at Denver.)

FIG. 2*A* and *B*. Roentgenograms of a 44-year-old woman who had extensive recurrent breast cancer involving the skin and subcutaneous tissues of the anterior chest wall, axilla, and supraclavicular space that had progressed during an adequate course of androgen therapy. An x-ray survey failed to reveal evidence of metastatic deposits in the skeleton as indicated by roentgenograms *A* and *C*, and an adrenalectomy-oophorectomy was carried out (she had received pelvic irradiation immediately following her mastectomy 3 years before).

FIG. 2*C* and *D*. A major regression of the soft tissue disease followed, but roentgenograms *B* and *D* taken 2½ months after the operation demonstrated four circumscribed areas of sclerosis, two in the right ilium and two in vertebral bodies. Repeat studies over the succeeding 3 months have shown no change in these areas, and the soft tissue disease has remained in a state of regression. It seems most likely that these four areas represent metastatic deposits in the medulla of the bone that were not discernible on the x-rays preoperatively but with the regression of the tumor and recalcification became manifest as areas of sclerosis. This patient remains in remission 16 months after adrenalectomy-oophorectomy and these skeletal lesions remain unchanged. (This patient was treated at the American Medical Center at Denver.)

then relapsed as therapy was continued. However, this phenomenon also occasionally occurs in patients who show no initial improvement as is illustrated in figure 1, and it seems rather probable that in such instances the administered hormone is effectively stimulating tumor growth. It might also be mentioned that the interpretation of changes in the bony skeleton as revealed in roentgenograms can at times be very difficult. Thus, the appearance of blastic areas in the skeleton where previously no lesions were evident does not necessarily indicate progression of disease. Such a case is illustrated in figure 2, where it seems evident that the newly appearing blastic areas represent the healing of pre-existing lesions in the bony skeleton that were undetectable by the usual radiographic techniques.

TYPES OF ENDOCRINE ALTERATIONS

A brief resumé of the most useful types of endocrine alterations effective in the temporary control of breast cancer is given below.

I. Ovariectomy or adequate ovarian irradiation[4, 15]
   - A. Useful by itself essentially only in women who are still menstruating or who have done so within the previous 6 months
   - B. Is followed by objective remissions in approximately 40 per cent of patients: site of metastases not particularly important in determining response although patients with significant hepatomegaly or central nervous system involvement are much less likely to respond favorably

C. Average duration of remissions 9 to 12 months
D. Is associated with relatively little morbidity
E. The response of the disease to this procedure gives important prognostic information when considering future endocrine manipulations

II. Androgen administration[1, 8, 13]
A. Can be used in patients of any age, but its use should be restricted to women after the menopause (natural or induced)
B. Incidence of objective regressions depends to some extent on location of metastatic deposits
1. Approximately 20 to 25 per cent of patients with superficial soft tissue disease or osseous metastases show objective improvement
2. Only about 7 per cent of patients with pulmonary and/or pleural lesions are improved
C. Median duration of response approximately 6 months
D. Is associated with a significant morbidity although this has been lessened by the development of a suitable orally active compound: occasional precipitation of hypercalcemia, a most serious sequella
E. Response or lack of response of disease to treatment is of relatively little prognostic value when considering further endocrine manipulations

III. Estrogen administration[1, 6, 7, 13]
A. Should be used only in patients who are 5 or more years past the menopause except under unusual circumstances
B. Incidence of remissions depends to a considerable degree upon the location of the lesions
1. Up to 50 per cent of patients with only the superficial soft tissues involved clinically will show significant regressions
2. About 35 per cent of patients with pulmonary and/or pleural involvement experience remissions
3. In only about 10 per cent of patients with osseous lesions will these lesions show healing
C. Mean duration of regressions is about one year with a median of about nine months
D. Associated morbidity is modest consisting mainly of fluid retention and initial nausea
E. Correlation of response to that following subsequent endocrine procedures not yet adequately tested (suggestively good in the case of subsequent hypophysectomy)

IV. Corticoid administration[10, 11]
A. Use generally reserved until late in course of disease; particularly useful in situations of hypercalcemia, impaired liver function, and central nervous system involvement
B. In most reports remissions obtained are short lived
C. Recommended doses produce changes similar to those of Cushing's syndrome
D. Acute "suppression test" felt by some to give prognostic information concerning response to adrenalectomy

V. Adrenalectomy and Hypophysectomy[2, 3, 5, 9, 12, 14]
A. Incidence of objective remissions is rather similar following these two procedures and is not greatly influenced by the age of the patient
B. Incidence of remission varies from 35 to 50 per cent depending somewhat upon the anatomical site of the involvement; in cases where the liver is considerably enlarged with cancer or there is significant brain involvement, regressions occur less frequently
C. Mean duration of remissions suggestively somewhat longer after hypophysectomy, but for both procedures it is in the vicinity of 9 to 12 months
D. Operative morbidity considerable, but decreases with increasing experience of the surgeon and the endocrinologist; still hospitalizations of from two to four weeks are the rule; once endocrine regulation has been achieved, controlling a patient of moderate intelligence is not too difficult

If the above outline is, in fact, a fair evaluation of the situation, we can begin to develop a rationale for therapy under a variety of circumstances. There remains, however, one important

consideration for which adequate data are not as yet available to warrant the drawing of a conclusion. It has not yet been established whether or not the length of palliation achieved by staged manipulations is greater or less than that resulting from an initial "massive assault." For example, we do not know whether women who are menstruating regularly obtain longer-lived palliation when endocrine therapy is initiated with an oophorectomy to be followed upon reactivation of the disease by adrenalectomy or hypophysectomy, or if an initial adrenalectomy-oophorectomy or hypophysectomy gives, on the average, the longer remission. Faced with this lack of knowledge, we prefer in general to initiate hormone therapy with the simpler maneuvers resorting to the more heroic measures only later on in the course of therapy. Because of this general plan, we like to start hormonal therapy rather early after dispersed recurrent and/or metastatic disease is demonstrated so that ample time is available to us to evaluate adequately one or more of the simpler procedures before we are forced to consider adrenalectomy or hypophysectomy. In addition, we advocate the early initiation of the simpler therapies, not waiting necessarily until significant symptoms occur, for to us it is more important to prevent symptoms from occurring than it is to alleviate them to varying degrees after they have appeared. This plan of postponing the major ablative procedures has yet another advantage. Although approximately 40 per cent of patients are materially benefited by these operations, and for these people the procedures are well worthwhile, for the remaining individuals they represent only an uncomfortable hospital stay. In our experience, these failures are better tolerated psychologically and do not appear to be so wasteful of time that could be spent at home when the patient already has significant symptoms or is faced with rather immediate disaster if the progression of the disease continues unabated. Furthermore, patients who are reluctant to have major operative procedures that are noncurative carried out at a time when they are essentially symptom free, will accept these procedures more readily as symptoms increase and are grateful when and if relief ensues.

It should be emphasized, however, that the major disadvantage to this approach is that, no matter how carefully one follows his patients, occasionally relatively rapid progression of disease may render a patient who is being treated with one of the simpler regimens totally unacceptable as an operative risk for one of the major ablative procedures.

Based entirely on the considerations touched on above, the following scheme of therapy is presented.

SPECIFIC THERAPY

Premenopausal women. If the patient has menstruated within the past 6 months or, having had a hysterectomy, has a cornified vaginal epithelium as revealed by vaginal smears and has had few or no menopausal symptoms, oophorectomy is carried out. In relatively few cases do we resort to ovarian irradiation because of the longer time required to effect a significant reduction in ovarian hormone production and the apparent advisability of removing the ovaries surgically at the time of a subsequent adrenalectomy should this procedure become indicated. If the patient's cancer does not show objective evidence of regression, adrenalectomy or hypophysectomy do not seem to us to be warranted because of the relatively low percentage of such patients that can be expected to show a favorable response to these major operative procedures. It has been suggested that in "castration failures" in whom many cornified cells remain in the vaginal smear following oophorectomy, one of these major ablative procedures may be indicated; but as yet, no data on this point are available. Since Treves and Finkbeiner[15] reported improvement in 5 of 31 "castration failures" with androgen therapy (this is as high a per cent of good responses as has been reported following adrenalectomy and hypophysectomy from the same institution), this relatively simpler form of therapy would appear to be the treatment of choice in this unfortunate group of patients. In patients who respond favorably to oophorectomy when reactivation of the disease occurs, androgen therapy is instituted before the major ablative procedures are considered if the disease is not too extensive and life threatening, but we proceed directly to adrenalectomy or hypophysectomy when the disease is extensive or when relatively vital areas such as the lung parenchyma are involved.

One-half to five years postmenopausal women. This is a rather unfortunate group of patients because the only relatively simple form of therapy available to them is the not-too-effective and

none-too-pleasant administration of androgenic hormones. However, it is our policy to start with this form of treatment in patients who do not have too extensive or life-threatening disease particularly when the superficial soft tissues of the body and/or the bony skeleton are the areas of primary involvement. When the disease progresses in the face of continued androgen therapy, whether or not the patient showed an initial regression, adrenalectomy or hypophysectomy is recommended to all patients who are adequate operative risks. If when first seen the patient's disease is extensive and/or life threatening, or involves the lung parenchyma, adrenalectomy-oophorectomy or hypophysectomy initiates our hormonal therapeutic attempt.

Five plus years postmenopausal women. When such women present with disease involving principally the superficial soft tissues of the body and/or the lung parenchyma or pleural surfaces, we feel that the statistical chance of improving the patient is essentially as good and the periods of regression obtained about as long with the administration of estrogen as with any other endocrine manipulation including hypophysectomy and adrenalectomy. In this group of women, we feel strongly that estrogen therapy is the initial treatment of choice. If the bony skelecton is involved to a considerable extent and the lungs are clear, we do, however, prefer to start therapy with the administration of androgens. Upon failure of treatment or reactivation of regressed disease, the course to follow is often difficult to decide. If the patient is in good physical condition, adrenalectomy or hypophysectomy is often indicated. It should be remembered, however, that a considerable number of patients who showed initial improvement will show a second regression upon the discontinuance of the additive therapy, particularly in the case of estrogen administration, without the institution of any other type of treatment so that a period of "no therapy" should usually preceed the beginning of a new therapy. Which major ablative procedure is preferable in the different situations has not yet been established, although Kennedy[8] has some indication that patients who have shown a good regression to estrogen therapy also tend to show good regressions following hypophysectomy. Since in this group of older patients many are poor operative risks for reasons other than their malignancy, it would be most helpful if an effective nonoperative therapy were available for use when estrogen or androgen administration fails. Possibly adrenal corticoid therapy will prove to be of significant help in such patients, and its use should be investigated more widely.

Although our knowledge of the usefulness of hormonal alterations in the treatment of advanced breast cancer continues to increase both in scope and in depth, there remain many unanswered questions. The above scheme is based essentially on statistical probability integrated to a degree with the morbidity inherent in the various procedures. How much better it would be if some relatively simple laboratory test could be developed for separating hormone-dependent from hormone-independent cancers of the breast. However, as yet no sufficiently reliable method save that of an adequate therapeutic trial exists. There are some positive correlations such as the period elapsing from mastectomy to the appearance of the recurrences or metastases, and possibly also the histologic appearance of tumor, but none of these have a high enough coefficient of correlation to withhold therapy from a person falling in the "low-expectancy" group with the probable exception of the "castration-failure" group. Of course, the biggest questions remain, "Why do certain breast cancers regress following alteration in the endocrine environment, and why do such regressed neoplasms again begin to proliferate?" Whether this latter phenomenon results from the cancer cells gaining autonomy or from some additional changes in the endocrine environment, such as an increase in the production of estrogens by the adrenals following ovarian removal, has not yet been clearly defined. However, in spite of the many unanswered questions, it remains a fact that good palliation, probably associated with a significant prolongation of life, can be achieved in approximately 40 per cent of patients with incurable breast cancer if the effective endocrine maneuvers that are available to us today are used wisely, and are not relegated to the role of a "final futile gesture."

Colorado General Hospital
Denver, Colorado

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PRIMARY TRACHEAL TUMORS

CHARLES MAXFIELD PARRISH, M.D., AND ROBERT E. JONES, M.D.

Salt Lake City, Utah

There has been considerable interest recently in primary tracheal tumors. Although these tumors are comparatively rare they command attention because of their dramatic symptomatology. Probably the main reason for the renewed interest is that these lesions are no longer the sole domain of the endoscopist.

Since the first report of a successful extensive tracheal reconstruction by Belsey[2] in 1946, a great deal of research has been done on this problem. The heretofore seemingly insurmountable technical problems have been taken to the laboratory and an increasing volume of reports of successful resection and reconstruction have subsequently entered the literature.

THE CLINICAL PROBLEM

Jackson's maxim that "all that wheezes is not asthma" is especially applicable to tracheal tumors. Unfortunately these mechanical symptoms and signs arise late in the course of disease since about 75 per cent of the tracheal lumen must be occluded before wheeze or dyspnea come to the foreground. Sometimes hemoptysis will lead to an early diagnosis.

The clinical reports are monotonously similar in describing the patient as having been followed and treated as an asthmatic. When stridor develops or symptoms of extension of tumor such as hoarseness and dysphagia, the diagnosis becomes more apparent.

The chest x-ray may be read as negative even in far advanced tracheal neoplasms. Bronchograms and tomograms are very accurate in the definition of tracheal lesions.

PATHOLOGY

It is interesting that tumors primary in the larynx above and the major bronchi below are very common, whereas the trachea in between is rarely the site of a primary neoplasm even though the histologic structure is similar.

By far the majority of tracheal tumors are malignant and the squamous carcinoma heads the list. The most interesting and next most common tumor is the cylindroma (fig. 1). This so-called adenoma probably arises from the mucous glands and is similar to the salivary tumor. Undoubtedly the cylindroma should be separated from the more benign carcinoid type of adenoma which occurs more toward the periphery of the lung. The cylindroma behaves much more like a low grade carcinoma with direct extension, lymphatic, and blood-borne metastases not uncommon.

TRACHEAL RECONSTRUCTION AND SURGICAL PROBLEMS

Experimental work and clinical results of tracheal repair and replacement stress that the trachea is both an air duct and a drain pipe. Any method of reconstruction that does not provide both of these requirements will fail.

Furthermore, both lateral rigidity and longitudinal flexibility are important. The repair must be airtight as well.

Tracheal resection has been thought doomed to failure because of alleged poor healing properties of this cartilage supported structure. The immediate technical difficulties of ventilation during the operative procedure are no longer a major problem. Furthermore all work has shown that the trachea has excellent healing properties under the proper conditions.

Without a doubt primary repair with end to end coaptation is the reconstruction procedure of choice. It has been shown that 30 to 40 per cent of the trachea can be resected as a sleeve with successful end to end suture anastomosis. In lower tracheal lesions the carina may also be removed, ventilating the left lung through the operative wound while attaching the right main bronchus to the tracheal stump. The left bronchus can then be sutured to the right bronchus as the right lung is ventilated through a long orobronchial tube.

In any tracheal anastomosis it is essential to bypass the glottis so that significant positive pressures during coughing cannot disrupt the suture line. Thus tracheostomy is an integral part of the procedure. It has been suggested that pneumoperitoneum will help to relieve

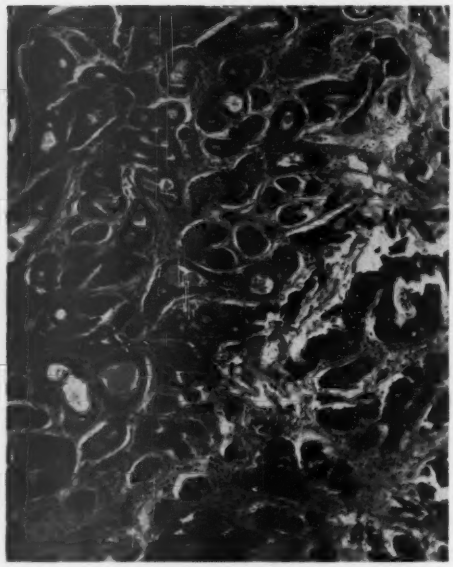

FIG. 1. Typical cylindromatous pattern

tension on the anastomosis by elevating the thoracic organs.

When it is necessary to remove only part of the tracheal wall, or a window, there have been several successful types of plastic repair depending upon the amount of remaining cartilaginous support. Fascial transplants and pedicled muscle-supported parietal pleura have been used.

The most difficult problem is that of substitution when an extensive tracheal resection has precluded coaptation despite full mobilization.

The difficulties arise from the fact that the ciliary carpet is interrupted, to interfere with the disposal of secretions. Furthermore we are dealing with an organ that is subject to the push and pull of respiration and intrathoracic pressure changes 20-odd times per minute. These phenomena lead to accumulation of secretions and loosening of prosthesis, especially of the solid type.

Certain principles have become obvious in the laboratory. If full replacement grafts are to be used they must be telescoped inside the tracheal ends to prevent granulation and fibrous ingrowth from these divided ends. Disproportion of prosthesis to trachea will again allow granulations to grow into the airway.

Tantalum mesh, wire mesh, lucite, vitallium, stainless steel, polyethelene, autogenous and homogenous tracheal grafts, pedicled skin, wire-reinforced dermis, and wire spring coils are among the many prostheses tried.

The principle of lateral stability and longitudinal flexibility is met by Belsey's fascial covered stainless steel spring coil. Also successful has been the polyethelene tube with generous sutures to surrounding structures and sometimes employing the Hufnagel principle of multiple point fixation at the ends.

PRESENTATION OF CASE OF CYLINDROMA

A 54-year-old woman with a background of two years chronic cough was admitted with a story of progressive asthmatic-type dyspnea of ten days duration. Routine bronchodilator medications failed to help, and the situation rapidly became very grave. Chest consultation resulted in rapidly transporting the patient to the operating room where, with the patient in extremis, a bronchoscope was rammed through an occluding tracheal mass with immediate complete alleviation.

Subsequent workup included tracheograms and esophagograms (figs. 2 and 3). Repeat bronchos-

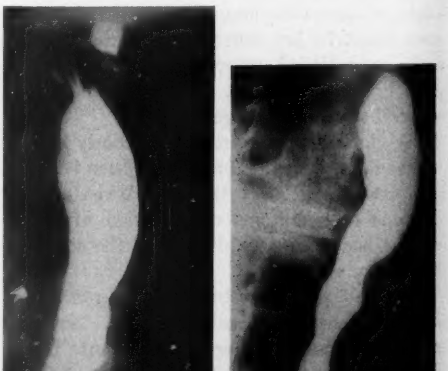

FIG. 2. Esophagogram showing posterior and lateral displacement indicating the degree of extrinsic involvement by malignant tracheal cylindroma.

FIG. 3. Tracheogram showing lower cylindromatous stricture.

copy was done with more adequate endoscopic removal with measurements of the lesion and existing anatomy performed for the anesthesiologist's use during operation. Pathologic report was malignant cylindroma.

Two preoperative findings of ominous import were subcutaneous emphysema immediately after the tumor was reamed out, and no visible tracheal cartilage rings above the proliferative tumor as visualized endoscopically.

Four days after the emergency brochoscopy a right thoracotomy and decortication of the right lung was performed. Considerable closed calcific apical tuberculosis was present with total pleural symphysis. The entire trachea from thoracic inlet to well beyond the tracheal bifurcation was mobilized. It was obvious that extratracheal spread was much more extensive than the endotracheal lesion. The cartilaginous support was completely destroyed from 1 cm. above the carina to well above the thoracic inlet. One lymph node showed metastatic tumor and multiple biopsies showed perineural and perivascular invasion. Multiple polyethylene and tygon tubes had been readied and a fascia lata strip had been taken immediately before thoracotomy, but since complete removal of the tumor was not possible it was felt resection was unwise.

On the fifth postoperative day radiotherapy was begun and a depth dose of 3000 r through anterior chest fields was done over a four-week period.

Bronchoscopy one month later showed a remarkable change. Although no tracheal cartilages could be seen and a rather intense endotracheitis was present, no tumor was visible and the lumen was essentially normal.

Bronchoscopy seven months later following an asymptomatic interim revealed essentially no change and no evidence of further growth. Tracheograms showed considerable resolution.

SUMMARY

Presentation of a case of primary tracheal malignant cylindroma is coupled with a review of the pertinent surgical problems of tracheal neoplasms.

Dr. Charles Maxfield Parrish
1046 East First South
Salt Lake City 2, Utah

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POST-TRAUMATIC INTUSSUSCEPTION IN ADULTS

JOHN A. DIXON, M.D.*

Ogden, Utah

Although a relatively common occurrence in childhood, intussusception in adults is comparatively infrequent. Dean and associates[5], report that approximately 5 per cent of all cases of intestinal obstruction are caused by intussusception. Of all cases of intussusception, 5 per cent occur in adults. "Idiopathic" or "primary" intussusception (*i.e.*, without associated polyp carcinoma, diverticulum, *et cetera*) in adults is even more rare. In Brown and Michels[2] report from the Cleveland Clinic, there were only 15 cases of intussusception in adults during a period in which 430,000 patients were admitted to their hospital. Of these 15 cases, only one was not associated with an obvious mechanical etiologic agent.

Various factors have been suggested as being productive of "primary" adult intussusceptions. Chaffin and Mason[3] have presented a series of 18 cases of intussusception occurring during pregnancy. Of this group, 10 were of the primary or idiopathic type. Allergy, dietary indiscretion and change in acid-base balance also have been vaguely implicated as predisposing conditions. The older literature mentions trauma rather prominently as a possible factor in the production of this lesion. In 1873 Lichtenstein[7] reported 176 cases of intussusception in adults of which 14 were noted following blunt trauma to the abdomen. Badertscher,[1] Falor,[6] and Cook[4] have each reported one case following abdominal injuries—an automobile accident, a gunshot wound of the abdomen, and a blow to the abdomen in a professional boxer preceding the intussusceptions described. Four cases of intussusception in adults have recently been encountered following various forms of abdominal and cerebral trauma. Although such a small number of cases certainly has no statistical significance, the very rarity of intussusception in adults in the absence of easily recognized causative factors leads us to consider the import of even a few such occurrences.

CASE REPORTS

Case 1. J. L., an 18-year-old white man, was admitted one hour following an altercation in which he received a .22 caliber gunshot wound in the right lower quadrant of the abdomen. At laparotomy two penetrating wounds of the cecum and a large retroperitoneal hematoma were found. On exploration of the small intestine an antegrade intussusception of the ileum was found approximately 30 cm. from the ileocecal valve. The intussusception was approximately 16 cm. in length. Upon reduction of the intussusception there was no evidence of direct trauma to the intestine. No intraluminal mass was palpable or visualized on transillumination. The perforations in the colon were sutured. The postoperative course was uneventful

Case 2. A 76-year-old man was struck by a truck while crossing the street. His injuries consisted of a severe abdominal contusion, a fracture of the left ulna, and a partial avulsion of the scalp. Shock and extreme abdominal rigidity were evident upon initial examination. At laparotomy he was found to have a transection of his transverse colon with gross peritoneal contamination. Exploration of the small bowel revealed an antegrade intussusception of the jejunum 28 cm. from the ligament of Trietz. The intussusception was 22 cm. in length and easily reduced. No tumor or trauma was noted in the region of the intussusception. The colon ends were exteriorized. The postoperative course was uneventful.

Case 3. A transorbital lobotomy was performed upon W. S., a 19-year-old white man with a diagnosis of paranoid schizophrenia. Six hours postoperatively he complained of severe crampy abdominal pain, nausea, and vomiting. He became moderately distended. Bowel sounds were present and slightly hypoactive. The picture for the next 5 days was one of intermittent partial bowel obstruction which roentgenographically was similar to that of a paralytic ileus. On the 7th postoperative day his distension increased and hyperactive bowel sounds were present. The following day he passed gas and a small amount of liquid stool. His distension decreased somewhat at this time. A moderate degree of fever and leukocytosis were noted until his 16th postoperative day when a picture of high grade intestinal obstruction was evident, and a tender mass was palpable on rectal examination. A laparotomy was performed and an antegrade intussusception of the ileum was found approximately 8 cm. from the ileocecal valve. The intussusception was 14 cm.

* Clinical instructor in Surgery, University of Utah College of Medicine, Salt Lake City, Utah.

in length, extremely firm, fibrotic and irreducible. Moderate dilation and hypertrophy of the proximal intestine was present. A resection of the ileum with anastomosis was performed. The postoperative course was uneventful. On examination the intussusception was found to present no tumor, diverticulum or leading point for the intussusception.

Case 4. R. T., a 43-year-old laborer, was involved in a trench cave in. He was buried to shoulder depth for a period of approximately one hour before being extricated. He was found to have fractures of the bodies of the second, third and fourth lumbar vertebrae. The pedicle of the second lumbar vertebra was avulsed. No neurologic abnormalities were present. There was evidence of a contusion of the abdomen in the right lower quadrant. Abdominal tenderness and spasm suggested a ruptured viscus. Laparotomy was performed. On opening the abdomen, a large right retroperitoneal hematoma was found which displaced the cecum anteriorly. On examination of the small bowel, three antegrade intussusceptions were found in the lower jejunum. Each of these was approximately 10 cm. in length and easily reduced. There was no evidence of tumor or local trauma to the intestine in these regions. The postoperative course was marked by evidence of intermittent partial small bowel obstruction. The patient's abdomen would become moderately distended and bowel sounds hyperactive. This would be followed by the passing of gas and semiformed stool with considerable relief of symptoms. The roentgenograms showed gas in the large and small bowel with varying degrees of small bowel distension. This sequence of events was repeated three times in the next 20 days; however, there was never a complete subsidence of symptoms. On the 21st postoperative day, a moderate degree of distension was noted associated with hyperactive bowel sounds. A Cantor tube was passed which appeared to be curled in a dilated segment of jejunum. A laparotomy was performed 24 days following his original injury, and an antegrade jejunal intussusception found 40 cm. below the ligament of Trietz. The intussusception was 13 cm. in length and not reducible. The proximal bowel was grossly dilated and hypertrophied. The intussusception was resected and an end-to-end anastomosis performed. Examination of the specimen showed no gross or microscopic tumor, diverticulum or obvious leading point. The postoperative course was uneventful.

DISCUSSION

Cases 1 and 2 presented no particular diagnostic or therapeutic problem. Definite indications for operation existed and the intussusception was an incidental finding. There was no evidence of recurrence following reduction.

Cases 3 and 4 presented very difficult diagnostic aspects. In both these instances, coexisting lesions were present which in themselves could account for some degree of ileus. These circumstances allowed obstructing intussusceptions to go unrecognized which really should have been suspected earlier. Case 4, in which an intussusception recurred postoperatively and required subsequent resection, seems unique in the available literature on this subject.

A fairly characteristic clinical picture emerges in the unrecognized cases which pursue a more prolonged course. Following a severe injury to the head, musculo-skeletal system, or abdomen, distension appears. The ileus first appears to be paralytic, then becomes intermittent and mechanical in nature. Nausea and vomiting seem somewhat less prominent than in the usual obstruction of comparable degree. The intermittent character of the obstruction is reminiscent of "gallstone ileus." The passage of flatus or even liquid stool frequently gives a false impression of remission and improvement. Blood in the rectum or stool is not noted and a palpable mass is present infrequently. Roentgenographic findings are not unusual except for the almost constant presence of some gas in the colon despite considerable small bowel distension and fluid levels. Fever and leukocytosis appear late in the course of events.

The mechanisms by which trauma might influence intussusception are largely conjectural at this time. Relative to the case which followed trans-orbital lobotomy, it is interesting to note that Watts[9] observed contraction and intussusception of the small intestine in monkeys upon electrical stimulation of the brain in the premotor area 7A. This response was largely abolished by bilateral vagotomy. Three dogs in his series of frontal lobotomies died of intussusception and intestinal obstruction.

In the other cases, direct trauma to the intestine or alterations in autonomic influences on peristalsis might be postulated. Starling and Bayliss[8] have shown that any stimulation of the intestinal wall will initiate a band of intense contraction just proximal to the point of stimulation. These bands sweep down the bowel for a variable

distance before disappearing. Such bands could conceivably become leading points for an intussusception. It must be stated, however, that there was no evidence of contusion, hematoma, or laceration at the site of intussusception in any of the cases in this series.

Traumatic or reflex alteration of the relative influence of the vagus nerve and sympathetic nerves controlling peristalsis could likewise be suggested as predisposing to intussusception.

SUMMARY

1. Intussusception in adults in the absence of carcinoma, diverticulum or other leading point is a rare disease.

2. Four cases of such intussusception following trauma are presented, one of which recurred following reduction and required subsequent resection.

3. Unrecognized intussusceptions produce a clinical picture of intermittent intestinal obstruction similar to that seen in "gallstone ileus."

4. Intussusception should be considered in all patients presenting this characteristic clinical syndrome following cerebral or abdominal trauma.

Virginia Bldg.
455 24th St.
Ogden, Utah

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LESIONS OF THE TERMINAL ILEUM AND COLON SIMULATING ACUTE APPENDICITIS

ROBERT WOODRUFF, M.D., AND ALBERT E. JAMES, M.D.

Denver, Colorado

Since an acute appendicitis is a relatively common surgical diagnosis, it is not surprising that the differential diagnosis between it and other acute pathologic conditions in the ileocecal region is at times confusing. In considering the diagnosis of acute appendicitis one must, of course, evaluate the clinical picture in order to rule out preoperatively other acute processes. This is, at times, difficult without exploratory laparotomy. If another intestinal lesion, other than acute appendicitis, is encountered, one should be prepared to carry out the most definitive surgical therapy consistent with a reasonable morbidity and mortality.

In our experience, the lesions of the colon and ileum most commonly encountered that simulate acute appendicitis are ileitis and ileocecitis, perforating and perforated diverticulitis of both the cecum and sigmoid, and carcinoma of the cecum or ascending colon. These lesions are not always entirely unsuspected before operation but often are seen unexpectedly.

From our files we wish to present cases to illustrate points in preoperative findings and our plan of surgical attack when these lesions are encountered. The postoperative course and results will be briefly discussed.

In Table 1 are cases of regional ileitis or ileocecitis which we encountered and feel are representative. Case 1 had had previous symptoms of gastrointestinal disturbance but only a two-day acute history with clinical and laboratory findings consistent with the diagnosis of acute appendicitis. He was explored as such, but with the findings of fairly localized regional ileitis, the terminal ileum and cecum were resected primarily. He has had no recurrent symptoms of the disease.

Case 2 had apparently had previous symptoms but was explored as an acute appendicitis although the use of a right rectus incision suggests that we were wary of our preoperative diagnosis. At surgery the differential diagnosis of lymphosarcoma and a fibrosing regional enteritis was considered, and a primary resection was carried out. The pathology report was that of a regional ileitis, and the subsequent course of the patient has suggested no recurrence.

Case 3 was that of a young woman whose preoperative findings were very consistent with appendicitis and she was explored as such. The appendix was found to be normal, but an inflammatory mass in the cecum was found which was difficult to differentiate entirely from a carcinoma. The terminal ileum and cecum were resected, and the pathologic report was an acute cecitis with ulceration through the cecal wall. Her postoperative course was uneventful, but she has since been lost to follow-up.

In table 2 are cases of diverticulitis which were confused with acute appendicitis and found to be otherwise at surgery. Case 1 was considered as an acute appendicitis with a fairly typical preoperative history and findings, and was seen first at the operating table in consultation. Resection of the terminal ileum and cecum was carried out for an acute suppurative diverticulitis of the cecum. Her postoperative course was complicated by a wound infection but she has since had no further difficulty.

Case 2 had findings of an acute abdomen not inconsistent with appendicitis although the leukocyte count was not abnormal. He responded well to resection for a ruptured diverticulum of the cecum. The postoperative course was without incident, and he has had no further trouble.

Case 3 is that of a patient in whom there was a three-day history of suprapubic pain with radiation into the rectum. His tenderness was just to the right of the midline in the lower abdomen. There was rectal tenderness with some suggestion of a mass. The leukocyte count was elevated. It is obvious that this was not the typical picture of appendicitis but certainly it was not ruled out before exploration. At surgery an inflammatory mass in the sigmoid, which was located on the right due to a long mesocolon, was found which was apparently due to perforation of

TABLE 1

Regional ileitis and cecitis

Case	Patient, Sex, and Age	Preoperative Findings	Surgical and Pathologic Findings	Postoperative Course and Complications	Result
1	D. S.; M; 31, 2/25/56	Cramps and severe pain with nausea and vomiting 2 days. Localized right lower quadrant tenderness. W.B.C., 14,800, 82% polys.	McBurney incision. Resection 18 in. ileum and cecum. Ileocolostomy. Regional ileitis	Hospital 6 days. Some cramping with foods 6 wk. No complications	No further gastrointestinal symptoms
2	E. B.; M; 40, 7/5/55	Abdominal cramps 4 days with anorexia. One attack 3 years before. Tenderness and cramps increased under observation in hospital. W.B.C., 14,300, 76% polys.	Rt. rectus incision. Resection 20 in. term. ileum and cecum. Ileocolostomy. Regional ileitis	Hospital 6 days. Occasional cramping with bulky foods. No complications	No further gastrointestinal symptoms
3	J. T.; F; 23, 6/10/53	Pain right lower quadrant 3 days. Preoperative nausea and vomiting. W.B.C., 21,000, 86% polys.	McBurney incision. Resection terminal ileum and cecum with ileocolostomy. Acute cecitis with ulceration through cecal wall	Hospital 7 days. No postoperative complications	Lost to follow-up

a diverticulum. After preparation of the bowel with Neomycin solution, a primary resection was carried out. The pathologic diagnosis was diverticulum of the sigmoid with acute perforation. His postoperative course was complicated by a partial wound separation which required closure, but was otherwise without incident.

Case 4 is that of a 51-year-old physician whose history, physical and laboratory tests prompted the diagnosis of acute appendicitis. At surgery he was found to have an inflammatory mass in the sigmoid with a long mesentery. This was apparently due to perforation of a diverticulum into the mesocolon. A primary resection was carried out, and the pathology was that of diverticulum of the sigmoid with acute perforation. His postoperative course was uncomplicated, and he has had no further gastrointestinal symptoms.

Another lesion in this area which can be encountered at exploration for acute appendicitis is that of carcinoma of the cecum. This has occurred less often in our experience but can present a picture simulating an acute appendicitis especially if an element of penetration or perforation has occurred. The case we present in this group (table 3) had symptoms longer than one would usually expect of appendicitis. He had small bowel distention and an intestinal tube was in place for decompression. X-ray of the colon had been interpreted as negative. Appendicitis was not the primary thought although the possibility of obstruction due to appendecial abscess was a consideration. At surgery he was found to have an obstructing lesion of the cecum, probably carcinoma. A right hemicolectomy and ileocolostomy was carried out. He had some postoperative ileus and developed a low grade wound infection, but has since had a normal recuperation.

SUMMARY

We have presented eight cases of diseases of the terminal ileum and colon which simulated acute appendicitis before surgical intervention. We presented our method of definitive surgical

TABLE 2

Diverticulitis

Case	Patient, Sex, and Age	Preoperative Findings	Surgical and Pathologic Findings	Postoperative Course and Complications	Result
1	J. D.; F; 36, 4/8/58	2 days abdominal pain. Nausea and vomiting. Localizing right lower quadrant pain. W.B.C., 13,000, 87% polys. Consult at table	Resection terminal ileum and cecum with ileocolostomy. Acute suppurative diverticulitis of cecum	13-day course with wound infection	No further trouble
2	J. O.; M; 41, 8/22/58	2 days right lower quadrant pain with nausea but no vomiting. Tender right lower quadrant. W.B.C., 7800, 76% polys.	Resection terminal ileum and cecum with ileocolostomy. Diverticulitis of cecum with rupture	Hospital 4 days. No complications	No gastrointestinal symptoms
3	R. V.; M; 47, 7/18/57	3-day history of suprapubic pain with radiation to rectum. Nausea but no vomiting. Tender just right of midline. W.B.C., 12,800	Inflammatory mass midsigmoid. 100 cc. 1% Neomycin instilled and resection carried out primarily. Diverticulitis of sigmoid with acute perforation	Hospital 7 days. Late wound separation	No symptoms referrable to bowel
4	F. J.; M; 51, 9/30/54	Severe right lower quadrant pain 5 hr. after 1½-days distress. No nausea or vomiting. Anorexia 24 hr. right lower quadrant tenderness with rebound. W.B.C., 9900, 71% polys.	Inflammatory mass sigmoid with apparent perforation into mesosigmoid. Resection of sigmoid primary. Diverticulitis of sigmoid with acute perforation	Hospital 10 days. No complications	No gastrointestinal symptoms

TABLE 3

Carcinoma

Case	Patient, Sex, and Age	Preoperative Findings	Surgical and Pathologic Findings	Postoperative Course and Complications	Result
1	C. F.; M; 58, 7/21/58	2 mo. intermittent cramp and abdominal pain. Vague tenderness. Flat plate showed small bowel distention. Previous Ba· E*i nterpreted as negative. Intestinal tube in place. Lab. negative	Right rectus incision. Right hemicolectomy with ileocolosto: :y. Carcinoma of cecum	Ileus and some fever. Low grade wound infection. Hospital 12 days	No further gastrointestinal symptoms

* Barium enema.

measures which have resulted in a reasonable morbidity and no mortality. Whether one utilizes primary resection, short circuiting procedures, or decompression with later definitive surgery, one should be prepared to proceed with such measures when exploring the abdomen for acute appendicitis.

Dr. Robert Woodruff
227 16th St.
Denver 2, Colorado

MESENTERIC VASCULAR OCCLUSION*

JOHN D. OLSON, M.D., AND FRANK M. LOCKWOOD, M.D.

Fort Smith, Arkansas

One of the most challenging situations encountered in abdominal surgery is that of mesenteric vascular occlusion. Most of the standard textbooks on surgery refer to it only briefly and in most discouraging terms, as the diagnosis is so often difficult to make and the mortality rate high. As late as 1942, the following statement was printed in a standard textbook of surgery;[3] "This disease is almost universally fatal and reports of recovery should be regarded with suspicion." The operative mortality for this disease appears to be in the neighborhood of about 70 per cent, according to Bancroft and Wade[1] in a collected series of cases. At the Mayo Clinic in Rochester, before 1938, Musgrove and Seybold[5] reported an operative mortality of 84.2 per cent. This was based on surgery of 19 patients, and of this number 16 died, giving this appalling mortality rate. However, out of 41 patients not operated upon there was 100 per cent mortality. Since 1938, however, there was reported a mortality rate of 23 per cent, 13 patients being operated upon with 10 survivals. Eleven patients not operated upon due to their extremely poor condition had a mortality of 100 per cent. In 1948 Benjamin[2] reviewed the literature and found only 116 successfully resected cases. I am sure there have been many more since then, and with the increasing percentage of geriatric patients we should keep this condition more in mind.

ETIOLOGY

Mesenteric vascular occlusion may be either arterial or venous, the latter type apparently being more frequent. Arterial occlusion is usually associated with auricular fibrillation or with arteriosclerotic plaques on which a thrombus forms in the superior mesenteric artery. There are a variety of predisposing factors for venous occlusion and these include hernia, adhesions, trauma to the mesentery at surgery, intra-abdominal infections, polycythemia vera, and blood dyscrasias.

*From the Holt-Krock Clinic, Fort Smith, Arkansas.

It is often difficult to determine at the time of surgery whether the lesion is actually arterial or venous in origin, as by the time these cases come to surgery both the arterial and venous supply may be involved.

DIAGNOSIS

It has been thought that it is difficult to make a diagnosis of mesenteric vascular occlusion preoperatively. This, perhaps, is because one is not usually thinking of the disease. It can simulate any surgical abdominal emergency, or even myocardial infarction. The symptomatology can be extremely varied. In arterial occlusion the onset is more dramatic in character, whereas venous occlusion may have an insidious onset and many hours may elapse before the seriousness of the illness is realized. Some of the most common symptoms on the arterial side are severe abdominal pain, which may be sharp or colicky in nature, a shock-like picture with the patient appearing critically ill, and possibly a bloody stool. Abdominal distention appears later. A primary venous thrombosis may start as vague abdominal distress, and it may take several days to develop the complete picture.

Physical findings are those of an abdominal catastrophe. Usually there is shock, extreme abdominal tenderness, sometimes a palpable boggy mass. Hyperactive bowel sounds of obstruction occur early, then a silent abdomen. Rebound phenomenon and muscle spasm may or may not be present. A bloody stool aids diagnosis when present.

The laboratory usually brings this diagnosis to mind, as gangrenous bowel gives a characteristically high leukocytosis. Leukocytes of 30,000 to 60,000 are not unusual. Early x-rays of the abdomen show little gas; later they may look like obstruction or ileus.

In general, with severe abdominal pain, shock, tenderness with palpable mass of distended bowel, extreme leukocytosis, one could consider mesenteric vascular occlusion.

TREATMENT

Early surgical intervention affords this group of patients the only hope for recovery. Shock is extreme and should be treated with vasopressors and intravenous fluids, but one should not spend too much time treating shock preparing for surgery. Here is one condition where it is often good practice to take a patient to surgery in shock; frequently the cardiovascular system stabilized after the dead bowel was removed. We like general anesthesia, and at surgery a wide resection of the involved bowel with primary end-to-end anastomosis is the treatment of choice. Careful evaluation of the bowel to be anastomosed should be done, as often the area of involvement spreads and a common cause for loss of the patient is breakdown of the anastomosis. Often the entire area supplied by the superior mesenteric artery must be resected. This includes the distal two-thirds of jejunum, all of the ileum and the right colon. Neomycin is injected into the lumen of the bowel. A Penrose drain is used so that any leakage of the anastomosis will be obvious.

There have been reports of successful extraction of a clot from the superior mesenteric artery.[4] Wise,[6] of Portland, Oregon, reported the third recorded case. This case was of a 65-year-old man who was in the hospital following gastric resection when an embolus hit the mesenteric artery. At exploration, the entire ileum and right colon were slate grey and pulseless. Following removal of clot, only one small area of ileum had to be resected. In our cases, the bowel was beyond salvage when explored, even if circulation could have been returned.

CASE REPORTS

Table 1 summarizes all cases operated by the authors in a 6-year period. There were 11 cases, 6 survivals, 5 deaths, for a 55 per cent survival rate.

Case 1. The patient was a 31-year-old women who noted abdominal cramping for 24 hours before admission. The day of admission she was seen by her physician, who told her she had a virus infection. The abdominal cramping persisted. She began to vomit and noted constipation. On admission to the hospital she complained of rather severe abdominal cramping and tenderness. Her menstrual periods had been somewhat irregular. She had started to menstruate the day before admission. Examination revealed an afebrile, young woman not appearing ill. Abdominal examination revealed slight tenderness in the right abdomen with questionable muscle guarding. No masses or organs were palpable. Bowel sounds were faint and hypoactive. Pelvic examination showed a uterus which seemed to be enlarged. No other pelvic masses. Leukocytes were 16,750 with 84 segs, 16 lymphs. Her red count was 4,700,000. A serum amylase was normal. Urinalysis normal. A flat plate of the abdomen revealed a considerable amount of feces throughout the colon and several gas-filled loops of small bowel in the upper abdomen.

A diagnosis of possible tubal pregnancy was made. The afternoon following admission, the patient suddenly went into deep shock. She was taken to the operating room with a diagnosis of hemorrhage from tubal pregnancy. At surgery, an extensive mesenteric occlusion was found, with gangrene of the small bowel, extending from midjejunum to terminal ileum. The gangrenous bowel was resected and an end-to-end anastomosis done. The patient made an uneventful recovery and was discharged 13 days after surgery. She has been followed since surgery and her general nutrition remains good, although she has had some difficulty keeping up her weight.

Case 2. Another interesting case was a 49-year-old man who was referred to us from a small local hospital. He had had approximately 15 feet of small bowel resected for mesenteric thrombosis. His convalescence was good until his 7th postoperative day when he suddenly became semicomatose, shocky, cold clammy. It was at this time that he was referred to us. When first seen, he was in deep shock, and dehydrated. Abdominal examination revealed a tender, palpable suprapubic mass extending up to the umbilicus. Auscultation revealed high pitched peristaltic sounds of obstruction. Temperature was normal. Leukocytes were 22,950, hemoglobin 14.5 gm., red blood cells 7,750,000. A preoperative diagnosis of extending mesenteric thrombosis was made and the patient was immediately prepared for surgery. At surgery, approximately 1½ feet of small bowel remained. The site of the previous anastomosis was disrupted and the terminal ileum and cecum were gangrenous. The remaining upper jejunum was dilated to approximately six inches in diameter. Approximately 6 inches of the remaining jejunum, along with the cecum, were resected and an end-to-end jejuno-ascending colostomy done. The patient did fairly well following surgery, although the blood pressure had to be maintained with Levophed solution. He did well for several days,

TABLE 1

Name	Age	W.B.C.	Flat Plate of Abdomen	Previous Surgery	Preoperative Diagnosis	Amount of Bowel Resected	Outcome
L. D. 82376 12-23-50	31	16,750	Gas-filled small bowel loops	Pelvic	Ruptured ectopic pregnancy	8–10 ft. jejunum and ileum	Survival
J. R. 91660 2-9-52	74	30,050	Single hair-pin loop. Strangulation	None	?Acute pancreatitis; ?mesenteric occlusion	All supplied by superior mesenteric artery	Expired
J. L. 2178-52	65	28,200	Distended upper small bowel loops. Obstruction	Pelvic appendectomy	Mesenteric occlusion	6–8 ft. ileum	Survival
A. H. 98027 4-7-53	59	31,150	Distended small bowel loops. Obstruction	Gastric resection. Appendectomy	Intestinal obstruction. ? Mesenteric occlusion	5 ft. mid-small bowel	Survival
R. A. 4067-53	6 mo.		Dilation of small bowel. Obstruction	Obstructing band (recent)	Intestinal obstruction	Distal half of jejunum and most of ileum	Expired (toxic hepatitis)
E. E. 103809 9-23-54	49	22,950		None	Extending mesenteric occlusion	All supplied by superior mesenteric vessels	Survival, 4–6 months
P. P. 101385 10-8-54	75	72,250		Radical proximal gastric resection (recent)	Mesenteric occlusion *vs.* peritonitis	All supplied by superior mesenteric artery	Expired
E. L. 105284 3-9-55	70	33,600	Distended small bowel loops (paralytic ileus)	None	Mesenteric vascular occlusion	All supplied by superior mesenteric vessels	Expired (toxic hepatitis and perforated ulcer)
H. S. 103318 8-7-54	72	13,850	Normal gas pattern	None	Diverticulitis, sigmoid	15 in.	Survival
W. A. B. 95783	64	17,400	Distended small bowel. Obstruction	None	Mesenteric occlusion	15 ft.	Expired
E. L. J. 1561200 10-3-51	57	38,900	No gas shadows	None	Ruptured viscus	Entire small bowel except distal 4 in.	Survival

the Levin tube being removed and the patient started on feedings. On the 5th postoperative day there was intestinal drainage about his abdominal drain, and it was obvious that he had an anastomotic leak. On the 6th postoperative day he was again explored, and it was found that the ascending colon was necrotic as well as the lower portion of remaining jejunum. Six more inches of jejunum were then removed along with the entire right colon, and the jejunum was anastomosed to the mid transverse colon by an end-to-end anastomosis. Again the patient required Levophed during the postoperative period. On the 5th postoperative day he again developed slight leakage with drainage of intestinal contents. However, he was able to eat and was having six to nine diarrheic stools per day. Maintenance of hydration and electrolyte balance was a difficult problem. This patient's fistula healed, and he was transferred to a University Medical Center where he lived for approximately 6 months. This patient had four inches of jejunum remaining below the ligament of Treitz and the left colon. His nutrition could not be maintained, and he died 6 months postoperatively of malnutrition.

Case 3. The last case, is that of a 64-year-old man who gave a history of gradual onset of mild midabdominal pain, weakness, profuse perspiration, nausea and vomiting. The pain persisted, and he was seen by his local physician, who diagnosed coronary thrombosis and referred him to the hospital with this diagnosis. The pain persisted and after several hours he was in an extremely shock-like state. When first seen his condition appeared critical. His pulse was extremely weak, and he was fibrillating. The abdomen was slightly distended, and bowel sounds were absent. The entire abdomen was extremely tender. A flat plate of the abdomen revealed a markedly distended upper small bowel, resembling small bowel obstruction. He was taken to surgery with a diagnosis of mesenteric occlusion. At surgery the entire small bowel was found to be gangrenous from a point 3 inches below the ligament of Treitz, down to the terminal ileum. Approximately 8 to 10 inches of normal terminal ileum remained. The involved intestine was resected. In this case, it was rather difficult to determine how far to carry the resection. However, palpation of the mesentery revealed multiple thrombosis. Recalling the previously discussed case, a wide resection was done with end-to-end anastomosis. This patient did extremely well postoperatively, and on the 2nd postoperative day the Levin tube was removed and the patient tolerated feedings. By the 4th postoperative day he was taking soft food, having eight to nine stools per day, was afebrile, and the abdomen dry. He seemed to be on the road to recovery, when on the 8th postoperative day he suddenly had severe chest pain, pallor, and died. He had continued to fibrillate throughout his postoperative course. The cause of death was a pulmonary embolus. This case demonstrates the difficulty in determining where to end the resection, and also illustrates a patient who was apparently recovering from his mesenteric occlusion and died of his original cardiac disease with fibrillation and further embolic phenomenon.

SUMMARY

We should be more aware of the possibility of mesenteric vascular occlusion. It is not a hopeless situation. It can simulate any acute abdominal catastrophe. The treatment is immediate surgery; wide resection is indicated. After recovery antidiarrheal medications and nutritional supplements are required.

Dr. John D. Olson
Holt-Krock Clinic
Fort Smith, Arkansas

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THE PROBLEM OF THE COMMON DUCT STONE: TRANSDUODENAL SPHINCTEROSTOMY VERSUS CHOLEDOCHOTOMY

RALPH R. COFFEY, M.D.

Kansas City, Missouri

This paper is presented in hope of stimulating reconsideration of the presently accepted methods of dealing with common duct stones.

In face of the statistics collected by Smith and associates[6] in exploration of the choledochus, stones are overlooked in 5.8 to 28 per cent of the cases, and we must conclude that the operation of choledochotomy alone for common duct stone is not a satisfactory operation. Also, statistics are reported by Diffenbaugh and Strohl[1] in which 50 per cent of the ducts explored on clinical evidences alone are unproductive of stone. Any operation which is performed with expectation of "cure," or removal of the pathologic condition, and which has such a poor record of satisfactory results, surely should be subjected to critical re-evaluation.

Full credence cannot be placed in the diagnostic reliability of the classical clinical symptoms and signs of common duct stone or in the reliability of positive or negative operative cholangiograms.

The diagnostic reliability of cystic duct cholangiography varies greatly with the techniques used and the diagnostic acumen of the radiologist and the surgeon involved. Personally, we believe under our present technique, that if the films suggest positive stone, it is 4 to 1 that the stone or stones are there and we will explore.

If clinical symptoms and x-ray both are positive we feel secure in exploration through the duodenum and performing sphincteroplasty. We also will explore in this manner if bile aspirated through the cystic duct cholangiogram "set up" is murky or contains debris.

Mixter and Hermanson[4] quote Lahey stating that, in a large series, 39 per cent of patients with proven common duct stones gave no history of jaundice.

For some years we have viewed with concern the rigid instruments which are used to "explore" this thin-walled, columnar mucosa-lined, yielding tube, whose contour has a "dog leg" in it, and which ends in a constricted sphincter mechanism of smooth muscle lined with mucosa (figs. 1 and 2). Rigid instruments in the hands of a determined operator certainly must at times wreak havoc with this rather frail duct and its lining.

The other factor in the present method of dealing with the problem of common duct stone is the ofttimes traumatic procedure of placing and leaving a T-tube in the common duct. This only produces drainage to the exterior of a body fluid intended by nature to be discharged within the intestinal tract.

FIG. 1. Cholangiogram through cystic duct. This is the anatomic structure!

Seldom does the T tube solve the problem of the retained duct stone or of the strictured sphincter of Oddi. It does act as a foreign body and unless properly cared for it may cause even more inflammation and damage to the duct, and could initiate formation of "new" stone.

The considered purpose of any operation for cholelithiasis or choledocholithiasis is to remove all stones from the biliary tract.

Paine and Firme[5] state that "95 per cent of the

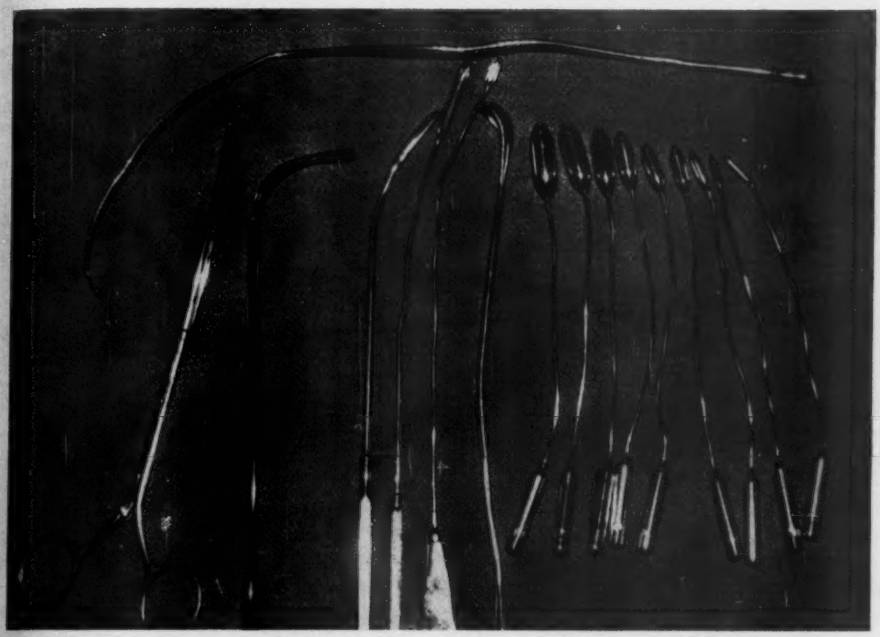

FIG. 2. Armamentarium. These are the instruments!

secondary operations on the bile ducts, and 88 per cent of biliary fistulae are due to retained stone." Under many circumstances transduodenal sphincterotomy is a much less traumatic procedure than choledochotomy and, properly performed, will assure that stones, if overlooked and remaining in the biliary tract, will pass into the duodenum. Certainly the stone impacted at the sphincter of Oddi may most simply be removed by this approach.

In sphincterostomy and intraduodenal exploration and drainage of the common duct the choledochal-duodenal juncture must be opened at the 10 o'clock position away from the possible common entrance of the duct of Wirsung.

The mucosa of the choledochus must be sutured to the duodenal mucosa step by step as the incision is enlarged, so that the caliber of the opening is as great as the distended common duct. This careful "step" suturing will obviate possible leak and control the field with minimal instrumentation.

The common duct may be irrigated from above through the ureteral catheter still in the cystic duct from the operative cholangiogram study, and irrigated and aspirated from below through a soft rubber or ureteral catheter. The technique of sphincterostomy is more fully covered in an earlier paper.

In the General Hospital service, where there are many intestinal wounds, the exploration through the duodenum, properly done, is not considered as dangerous as exploring the thin-walled common duct. Sphincteroplasty leaves the patient with bile properly draining into his intestinal tract and if stones are still in the upper ducts there is some assurance he can rid himself of them spontaneously.

Judd and Marshall[2] reported in 1930 that they had in four cases successfully removed stones by transduodenal choledochotomy which they could not remove by choledochotomy alone.

McManus[3] in 1892 reported opening the duodenum opposite the entrance of the common duct, incising the opening of the duct, and successfully removing an impacted stone, apparently with no other drainage of the common duct mentioned.

Since 1877 when Charcot (See McManus[3]) published the "Classical Syndrome of Common Duct Stones" many methods of dealing with the

problem have been described from Tait, 1884, crushing the stones in the ducts with padded forceps to Colp, 1938, describing an endocholedochal blind sphincterotomy, with special sphincterotome. This is an ingenious but rather "blind" approach to the anatomical goal.

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WOUND HEALING. III. ARTIFICIAL MATURATION OF ARRESTED REGENERATE WITH AN ACETYLATED AMINO SUGAR[a]

B. L. Reynolds, M.D., Theodore F. Leveque, Ph.D.,[b] and Robert W. Buxton, M.D.

Baltimore, Maryland

In a recent report[1] we suggested that a layer of "organizer cells" beneath the advancing edge of an open wound is responsible for the initiation and control of the phenomena which are the essential components of repair: contraction, migration of regenerate, fibrosis, and epithelization (fig. 1). By injecting an oxidative phosphorylating uncoupling agent, dinitrophenol (DNP), directly into the organizer cell layer, we produced a chemical arrest of healing without causing traumatic disruption of morphology that would follow mechanical excision of that layer. Counter administration of an acetylated amino sugar, *N*-acetyl D-glucosamine (NADG)[c] with adenosine 5-monophosphate (AMP),[d] into the organizer cells resulted in their partial metabolic recovery from the uncoupling agent, accompanied by the appearance in the hypodermis of mast cells in large numbers with prominent granules. As recovery continued, cellular activity increased in the migratory regenerate, and fibrosis, particularly collagen, appeared.

In our preparations 48 hours were required before the uncoupling agent arrested contraction. During this time, migration of regenerate had begun, but it was also arrested as the uncoupling material was continued.

Since the process of healing was re-established by the direct administration of an acetylated amino sugar to the organizer cell layer, it was of interest to determine what effects the same amino sugar would have upon the regenerate which had already migrated before its arrest by DNP. Studies have been carried out to demonstrate such effects and this report describes the results of those studies.

[a] From the Departments of Surgery and of Anatomy, The University of Maryland School of Medicine, and The University Hospital, Baltimore 1, Maryland.

[b] Supported in part by Grant B1013, U. S. P. H. S.

[c] The *N*-acetyl D-glucosamine utilized in this study was provided by Chas. Pfizer and Company, Inc., Brooklyn, N. Y.

[d] The adenosine 5-monophosphate in this study was supplied as My-B-Den by Ames Inc., Elkhart, Ind.

Prepared for the Southern Society of Clinical Surgeons Meeting on May 5, 1959, at University of Maryland Hospital, Baltimore, Maryland.

METHOD

Fifty male Wistar albino rats weighing between 150 and 200 gm. were individually caged for three weeks in the environmental conditions of our laboratory. All animals received laboratory chow diets and tap water *ad libitum*. For contraction studies we placed the wound on the right dorsum of each animal as reported previously.[1] On the day of wounding and on each subsequent 24-hour period DNP, 100 mg./kg., was injected into the organizer cell layer beneath the margins of the wound edge. On the 3rd post-wounding day and in each subsequent 24-hour interval NADG, 3.0 gm./kg., and AMP, 100 mg./kg., were injected in the migratory regenerate formed before the arrest of contraction.

Immediately after wounding and in each subsequent 24-hour period representative but randomly selected animals were weighed and sacrificed.

Gross analysis of contraction. Following sacrifice, eschars were gently removed and evaluation made of decrease in void. This was carried out by a photographic technique previously described.[1]

Microscopic examination of tissue. The entire wound area within epilation was excised to and including fascia and muscle. This preparation was spread on cork containers and fixed in Zenker-formal solution. A specimen of distal skin and hypodermis from the left upper extremity was similarly fixed. All sections were stained with chrysoidin and counterstained with either hematoxylin and eosin or Foot's modification of Masson's trichrome stain.

Chemical analysis of healing. Hexosamine was determined by a modified Elson-Morgan reaction. Collagen was determined by analysis of hydroxyproline. Lactic acid was determined by a method devised in this laboratory.[1]

RESULTS

The results are shown in figures 2 through 11. Following the pattern of our previous investigations, contraction of the wound edges had virtually ceased by the 2nd day of DNP administration (fig. 2). Within 24 hours of injection of NADG into the arrested migratory regenerate cell activity had returned as evidenced by the "movement" of fibroblasts and the beginning of fibrosis (fig. 7). From the 4th to the 10th post-wounding day, fibrosis increased with such rapidity that the cellular elements in the regenerate seemed to be greatly decreased in number (fig. 9). During this time resumption of contraction began, probably from the effects of diffusion of injected NADG into the organizer cell layer, and by the 16th post-wounding day, or the termination of this experiment, the contraction process approached 30 per cent of closure (fig. 2).

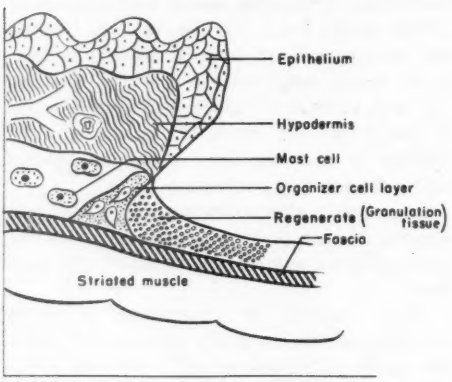


FIG. 1. Diagrammatic section through tissues of an open contracting skin wound.

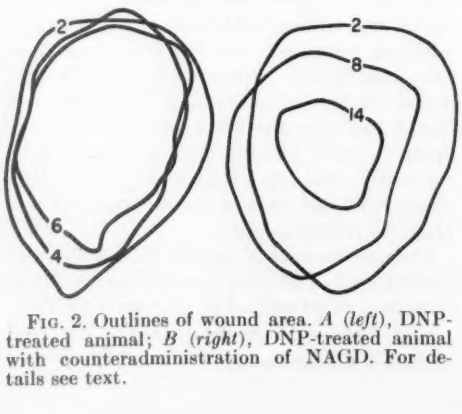


FIG. 2. Outlines of wound area. *A* (*left*), DNP-treated animal; *B* (*right*), DNP-treated animal with counteradministration of NAGD. For details see text.

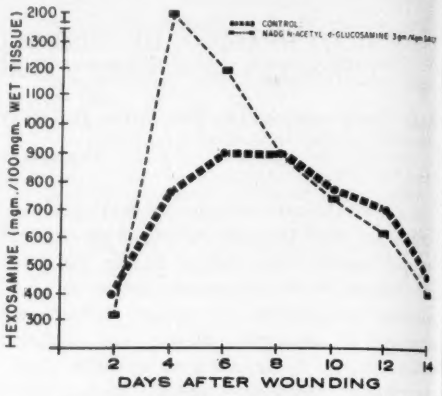


FIG. 3. Hexosamine determinations; regenerate

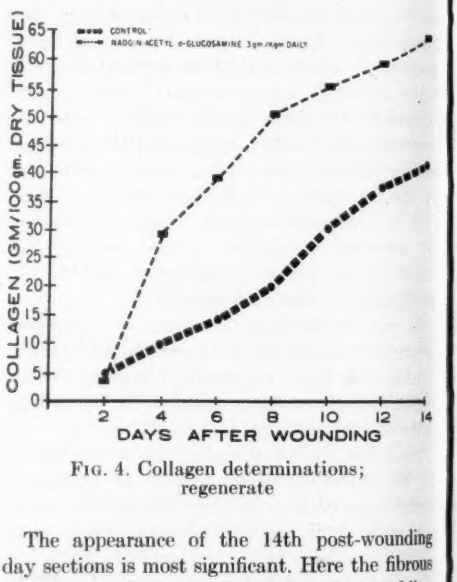


FIG. 4. Collagen determinations; regenerate

The appearance of the 14th post-wounding day sections is most significant. Here the fibrous elements are extremely disorganized resembling the picture seen in keloid formation (fig. 10). Attempts at organization of the stroma, evident as late as the 6th post-wounding day, have entirely disappeared (fig. 9). Analytic studies revealed a considerable portion of this fibrous material to be collagen (fig. 4). At this time random activity of the process had so increased that invasion of fascia and muscle had occurred.

Local tissue response was unusual in that the wound area was extruded as a pedicle, as if the host animal were rejecting the wound and its

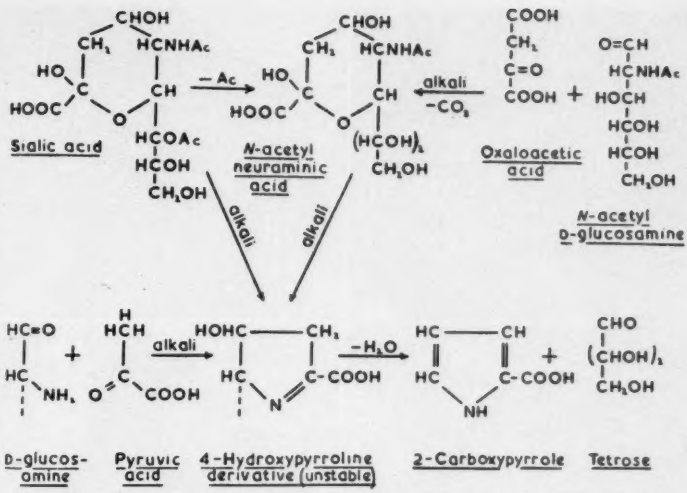


FIG. 5. Formation of hydroxypyrrols from sialicates (after Gottschalk)

products. Necrosis with infection was present in large areas of this very rapidly developing regenerate (fig. 10).

As early as 24 hours after the administration of NADG, mast cells were present in great numbers in the connective tissue immediately adjacent to the migratory regenerate. These cells were rather characteristic by their lack of affinity for the chrysoidin stain. From the 2nd day of NADG administration the mast cells gradually decreased in number so that by the 6th day practically none could be seen. However, as the number of cells decreased, the stainability of these cells was enhanced. This was particularly striking in the 4th day of administration of the amino sugar. It is of interest to note that this phenomenon could also be observed in tissues taken from the contralateral upper extremity.

Chemical evaluation confirmed the morphologic findings. Hexosamine levels increased rapidly with the direct administration of amino sugar (fig. 3). Although the peak values occurred between the 3rd and 5th post-wounding days, elevated levels continued quite longer than in controls. With the onset of dense fibrosis, as indicated by collagen concentration (fig. 4) and microscopic appearance of the regenerate (fig. 8), hexosamine concentration decreased (fig. 3). By the termination of this experiment collagen concentration exceeded skin normals (fig. 4).

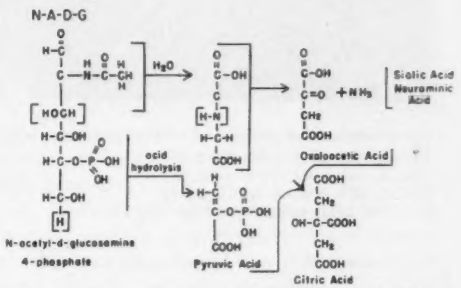
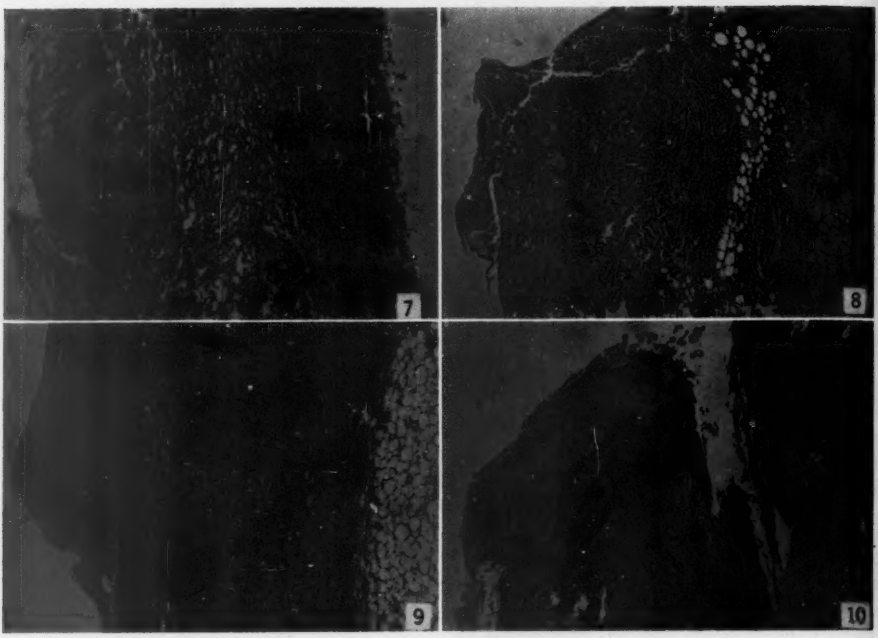


FIG. 6. Suggested synthesis of critic acid from *N*-acetyl D-glucosamine

DISCUSSION

Morphologic and chemical analyses indicate that by using an appropriate acetylated amino sugar, NADG, enhancement of cell activity and maturation of fibers does occur in regenerate in which organizer cells have been treated with uncoupling agents, producing arrest of normal contraction and of migration. When maturation had reached an expansive state, diffusion of NADG into the organizer cell segment at the periphery of the wound resulted in a resumption of contraction although the latter process was markedly reduced. The highly disorganized pattern of this artificially matured regenerate demonstrated what may happen in an arrested migratory regenerate when artificial metabolites are provided but removed from the effects of the



FIGS. 7, 8, 9, 10
Color photomicrographs of wound area and adjacent tissue.
FIG. 7. 2nd post-wounding day.
FIG. 8. 4th post-wounding day.
FIG. 9. 6th post-wounding day.
FIG. 10. 14th post-wounding day.

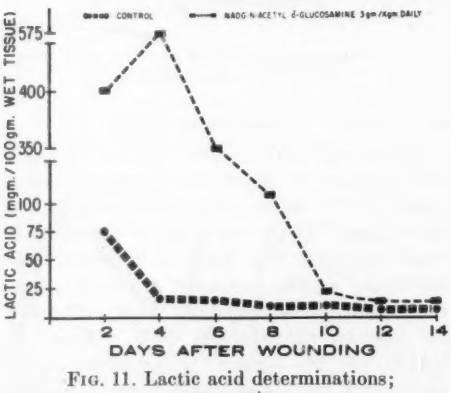


FIG. 11. Lactic acid determinations; regenerate

organizer cell groups. This seems further confirmation that in addition to initiation of the process of contraction and migration of regenerate, the organizer cells also control the integration of elements of repair.

Prompt rise in hexosamine with subsequent increase in collagen content of arrested regenerate following NADG administration implicates this acetylated amino sugar in the formation of extracellular mucopolysaccharides and glycoproteins. Hexosamine concentration in regenerate includes free and bound moieties. Although there is an initial rise in free hexosamine as would be expected from NADG administration, from the 6th day bound hexosamine fraction predominates. In the presence of cellular elements of regenerate, NADG may combine with oxaloacetic acid to produce neuraminic acid in extracellular substance; with further acetylation of the 6th carbon, sialic acid is formed (fig. 5). Sialicates occur in ground substance in quantity and are implicated in collagen protein synthesis in an alkaline medium by forming unstable hydroxypyrrols which upon condensation yield loose collagen matrices (fig. 5). Stain techniques for collagen and mucopolysaccharides confirm these analytical findings.

Watts and associates,[3] quoting Dunphy, have suggested that uronic acid determinations more nearly represent true mucopolysaccharide concentrations. However, Shetlar and his associates[2] point out that concentrations of uronic acid containing polysaccharides never exceed those of hexosamine in open wounds and occur in greatest concentration just before wound closure. It is our impression that uronic acid-identifiable polysaccharides are important in absorption and retraction of regenerate. Isotope studies with the latter group and with hydroxypyrrols are underway to investigate these relationships.

Demonstration of rapid increase in cell activity of regenerate following NADG administration also implicates this amino sugar in intracellular energy sequences. One possible pathway is suggested in figure 6 in which acid hydrolysis and deacetylation of NADG may produce pyruvate and oxaloacetate with condensation to citric acid. Fall in lactic acid concentration of regenerate (fig. 11) following NADG is compatible with this hypothesis, indicating an increased level of oxidation. Lactic acid accumulation may indicate a block in conversion of intermediary metabolites to three carbon compounds or an uncoupling of phosphate bonds with the production of heat. This hypergic energy situation prevails with mechanical or chemical trauma, resulting in disorganized protoplasm. If the trauma is severe enough with the disruption of cytoplasm and cell content, necrosis is the inevitable consequence. There are a considerable number of cells contiguous to those actually necrosed whose cytoplasm is still intact; in these, the greatest effect is manifested by the disruption of its enzyme systems. The structural enzyme systems are most greatly and initially affected, particularly the mitochondrial and juxtanuclear systems. These enzyme systems are responsible for oxidative phosphorylation and for the active transfer of energy from one molecule to another. Until organelle and cytoplasmic rearrangement occurs, the cell functions on a low energy system; a lag interval results. The period of rapid growth which follows this interval suggests an attempt of the organism to compensate for a low energy situation. Providing cells of a regenerate with NADG results apparently in oxidative activity with earlier recovery from the chemical trauma exercised by dinitrophenol (DNP).

The acetylated amino sugar, NADG, is the only material which has produced such effects in our laboratory, although glucose, glucose and fructose phosphates, and glucosamine have been similarly evaluated. Addition of adequate quantities of NADG to a nonuncoupled animal should result in a satisfactory supply of exogenous energy to traumatized cells from elective or traumatic wounds. Such studies with the addition of more active phosphate compounds than AMP, are the subjects of a later report.

SUMMARY

1. *N*-Acetyl D-glucosamine is capable of enhancement of cellular action and fibrosis in an arrested regenerate, and it seems involved in both intra- and extracellular reactions.

2. If the arrested regenerate is removed from the control of the organizer cell layer in the open wound, artificial maturation of that regenerate results in a highly disorganized stroma which the host animal subsequently attempts to reject.

3. Our findings would seem to substantiate further the suggestion that the organizer cell is responsible for the initiation, control and integration of most elements of repair in an open skin wound.

4. Attempts at influencing traumatized cells in open wounds of noncoupled animals seems possible with the use of the acetylated amino sugar NADG and may represent a means of reducing post-traumatic lag of hypergism.

Dr. B. L. Reynolds
Department of Surgery
University Hospital
Baltimore 1, Maryland

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SURGICAL TREATMENT OF CARCINOMA OF THE THYROID

JOSEPH P. MCNEILL, M.D., AND JOHN V. GOODE, M.D.

Dallas, Texas

The problems in the surgical treatment of carcinoma of the thyroid have not yet been solved. This statement is supported by the fact that there is still a wide divergence of opinion among experienced surgeons concerning the best method of treatment of this disease. Crile[1] has advocated marked conservatism, whereas the Lahey Clinic,[2] on the other hand, has attacked the problem in a very radical manner. Reports from both centers apparently are equally good. In between these extremes of treatment, many variations are advocated.

This report presents the authors' total experience with carcinoma of the thyroid. It is based on a study of 37 patients treated surgically for the disease over a period of 25 years. Because the series is small, a statistical analysis would be insignificant. Therefore, this report, with a 100 per cent follow-up, will be confined to a study of the types of tumors encountered, the degree of spread, types of treatment employed, and the results of treatment.

Table 1 contains a classification of the various types of carcinoma of the thyroid that were encountered in this series. Of the 21 papillary carcinomas of the thyroid, ⅔ had extended beyond the thyroid to regional nodes. Of the 7 alveolar adenocarcinomas, 4 had extended beyond the thyroid. Of the 7 highly malignant adenocarcinomas, including small cell and epidermoid carcinomas, all had extended beyond the thyroid, either by direct invasion or to regional nodes. The two Hurthle cell carcinomas were confined to the thyroid. Of the entire group, there were 2 children with carcinoma of the thyroid, one of whom had received x-ray therapy to her thymus as an infant.

The methods of treatment in this series are listed in table 2, and will be noted to have varied considerably throughout the years. The results obtained from experience with these various plans has led to the following recommendations in the treatment of carcinoma of the thyroid.

It appears mandatory that bilateral total thyroidectomy be carried out in each instance, even though macroscopic tumor is present only on one side. Formerly, only a total lobectomy on the affected side was performed. One reason for this change is the fact that 3 patients were encountered who developed tumor in the opposite lobe, one, two, and three years after the initial operation. Another reason for advocating total removal of both lobes of the thyroid is the possibility that radioactive thyroid therapy might be indicated in treatment of distant metastases in these functional tumors.

Patients with highly malignant anaplastic small cell adenocarcinoma of the thyroid, when feasible, have been subjected to total thyroidectomy, radical neck dissection on the affected side, and postoperative deep x-ray therapy. The rationale for this recommendation was based on the 5-year survival, without evidence of recurrence, of two patients from this series treated in this manner.

It will be noted in table 2 that limited cervical lymph adenectomy, or the so-called "picking" operation, was performed on 12 patients with metastatic papillary or follicular adenocarcinoma, and only 2 radical neck dissections were done. One of these 2 patients was a physician's relative, the other a nurse. Unusual pressure from the large number of consultants in each case resulted in the decision to carry out this procedure, even though it did not appear to the surgeon that such a radical procedure was indicated.

In all, 14 patients received postoperative deep x-ray therapy. Of these, 4 had small undifferentiated carcinoma; the other 10 received x-ray therapy either early in this series or because it was technically impossible to remove all of the gross tumor. At the present time, it is recommended that postoperative x-ray therapy be withheld from the patient with either alveolar or papillary adenocarcinoma unless all gross tumor cannot be removed surgically.

The results of treatment of 21 patients with papillary adenocarcinoma of the thyroid are listed in table 3. It will be noted that 11 patients are alive after from 6 to 20 years, and 2 patients are alive after from 5 to 10 years, without evidence of recurrence; 4 are known to be dead,

TABLE 1

Carcinoma of the thyroid

Papillary		21
Confined to thyroid	7	
Extended beyond thyroid	14	
Alveolar		7
Confined to thyroid	3	
Extended beyond thyroid	4	
Highly malignant adenocarcinoma		7
Confined to thyroid	0	
Extended beyond thyroid	7	
Hurthle cell carcinoma		2
Confined to thyroid	2	
Extended beyond thyroid	0	
Total		37

TABLE 2

Treatment

Figures in last column represent number of years after surgery.

	No. of Cases	Follow-up
Radical neck dissection	4	
Small cell (Mr. C. and Mrs. S.)	2	
"Picking" dissection	12	17, 7, 7, 7, 6, 6, 6, 5, 18 mo., died 6 mo., died 1 yr., died 1 yr.
Postoperative x-ray therapy		
Papillary	5	20, 6, 6, 3 mo., died 1 yr.
Hurthle cell	1	5
Small undifferentiated	4	6, 5, died 1 yr., died 2 yr.

and 4 have been followed less than 5 years. This group includes 2 patients with diagnosis of lateral aberrant thyroid at a time when this diagnosis was not known to represent metastases from papillary adenocarcinoma of the thyroid. Both of these patients were treated with excision of the involved lymph node only. One died 4 years after the removal of this node, with essential hypertension, from which he had suffered for some 10 years; the second is alive 14 years after excision of the node. She was not followed until

TABLE 3

Results in papillary carcinoma

Figures in last column represent number of years after surgery.

	No. of Cases	Follow-up
Papillary	21	
Known dead	4	
Alive 5 plus years without evidence of disease	11	20, 18, 9, 8, 8, 7, 7, 6, 6, 6, 6
Alive 5 years with evidence of disease	2	
Too soon for follow-up	4	3, 2, 2, 3 mo.

TABLE 4

Results in alveolar cell carcinoma

Figures in last column represent number of years after surgery.

	No. of Cases	Follow-up
Alveolar cell carcinoma	7	
Died of disease	1	
Alive 5 plus years without evidence of disease	5	7, 7, 6, 6, 5
Too soon for follow-up	1	2

TABLE 5

Results in Hurthle cell carcinoma

Figures in last column represent number of years after surgery.

	No. of Cases	Follow-up
Hurthle cell carcinoma	2	
Alive 5 years without evidence of disease	2	5, 5
Highly malignant	7	
Dead	5	
Alive 5 years without evidence of disease	2	6, 5

work was begun on this study, at which time she was called in and found to be asymptomatic; however, she did have an enlarged, hard, and nodular thyroid on the affected side. No other masses could be appreciated. She was advised to have this removed, but has not yet consented to do so.

The results in treatment of 7 patients with

alveolar cell carcinoma are listed in table 4. One died of the disease, whereas 5 are alive after from 5 to 7 years after surgery without evidence of recurrence. One has been followed less than 5 years.

The results of treatment of patients with Hurthle cell carcinoma and highly malignant carcinoma of the thyroid are listed in table 5. Of the 2 patients with Hurthle cell carcinoma, both are alive 5 years without evidence of the disease. Of those with highly malignant disease, 5 are known to be dead, and 2 are alive 5 years following treatment without evidence of recurrence.

An analysis of the 10 deaths of this series is of interest. All 5 of the patients who died with undifferentiated carcinoma of the thyroid died of their disease within 2 years after surgery. One patient with follicular carcinoma of the thyroid died of his disease 6 months after surgery. There were 4 patients who died with papillary carcinoma of the thyroid within 14 months to 5 years after surgery. Two died with evidence of brain metastases and 2 died of cerebral vascular accidents.

The authors' experience with radioactive iodine in the diagnostic and therapeutic management of this disease is limited to 2 patients. One developed a metastasis to the lumbar spine, which was diagnosed by a radioactive iodine uptake study; palliation was successful for 1 year after radioactive iodine therapy. Another patient with papillary adenocarcinoma of the thyroid was found to have a large area in the pelvis which picked up a diagnostic dose of radioactive iodine. At surgery, this was found to be a large benign serous cyst of the left ovary, which bears out the fact that cystic fluid accumulation in the body will pick up radioactive iodine.

SUMMARY

This report consists of a follow-up on 37 patients treated surgically for carcinoma of the thyroid. In the series, there were 21 papillary adenocarcinomas, 7 alveolar adenocarcinomas, 7 highly malignant carcinomas, and 2 Hurthle cell carcinomas. Because the series is small, statistical analysis of the results is insignificant; however, it is of special interest because of the completeness of the follow-up.

Conservative treatment was used in most instances, except for the highly malignant group. Two patients with highly malignant small cell adenocarcinoma with spread to the regional nodes have been followed for over 5 years without evidence of recurrence. Follow-up report is also made on 2 patients with papillary adenocarcinoma treated only with excision of lateral metastatic nodes, at a time when these nodes were considered to be lateral aberrant thyroid tissue. The authors' current management of this disease has been presented, which is based on a follow-up study of the patients presented. The changes in management of this disease are explained on the basis of follow-up examination of patients presented in this series.

Dr. Joseph P. McNeill
3707 Gaston Ave.
Dallas 10, Texas

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Book Reviews

The editors of THE AMERICAN SURGEON *will at all times welcome new books in the field of surgery and will acknowledge their receipt in these pages. The editors do not, however, agree to review all books that have been submitted without solicitation.*

Textbook of Oral Surgery. Edited by GUSTAV O. KRUGER, B.S., A.M., D.D.S., F.A.C.D. The C. V. Mosby Company, St. Louis, 1959.

This is an excellent textbook as well as a very satisfactory reference for the oral surgeon and the general surgeon interested in problems of the face and jaws. There are excellent sections by outstanding contributors with very satisfactory presentations of basic surgical subjects such as "Surgical Technique," "Surgical Bacteriology," "Hemorrhage and Shock." In addition to a very satisfactory coverage of frequently encountered problems about the face and jaw, special attention is directed toward acquired defects of the hard and soft tissues of the face, developmental deformities of the jaw, and the problem presented by salivary gland and duct pathology. This book is extremely well illustrated with comprehensive and convenient cross-indexing. Each chapter is supplemented by a reference list that should be of great value to the reader interested in a specific phase of the material included.

The drawings by Biagio J. Melloni are clear, concise and very informative. It is recommended for the dental student and the oral surgeon.

GEORGE H. YEAGER, M.D.

The Plasma Proteins: Clinical Significance. By PAUL G. WEIL, M.D., Ph.D. J. B. Lippincott Company, Philadelphia, 1958–1959.

Dr. Weil's monograph is a short, concise presentation of a broad and difficult subject. Written in lecture form in semi-outline style, it is easy to read and the illustrations are adequate. Although shallow in controversial subject matter, it is generally informative and certainly sufficiently detailed for the practicing physician or student. There are 133 pages divided into 21 chapters covering laboratory methods, normal proteins with their aberrations, and abnormally occurring proteins. Specific disease entities are discussed, and included are interesting chapters on proteins in the aged patient and in those with liver disease.

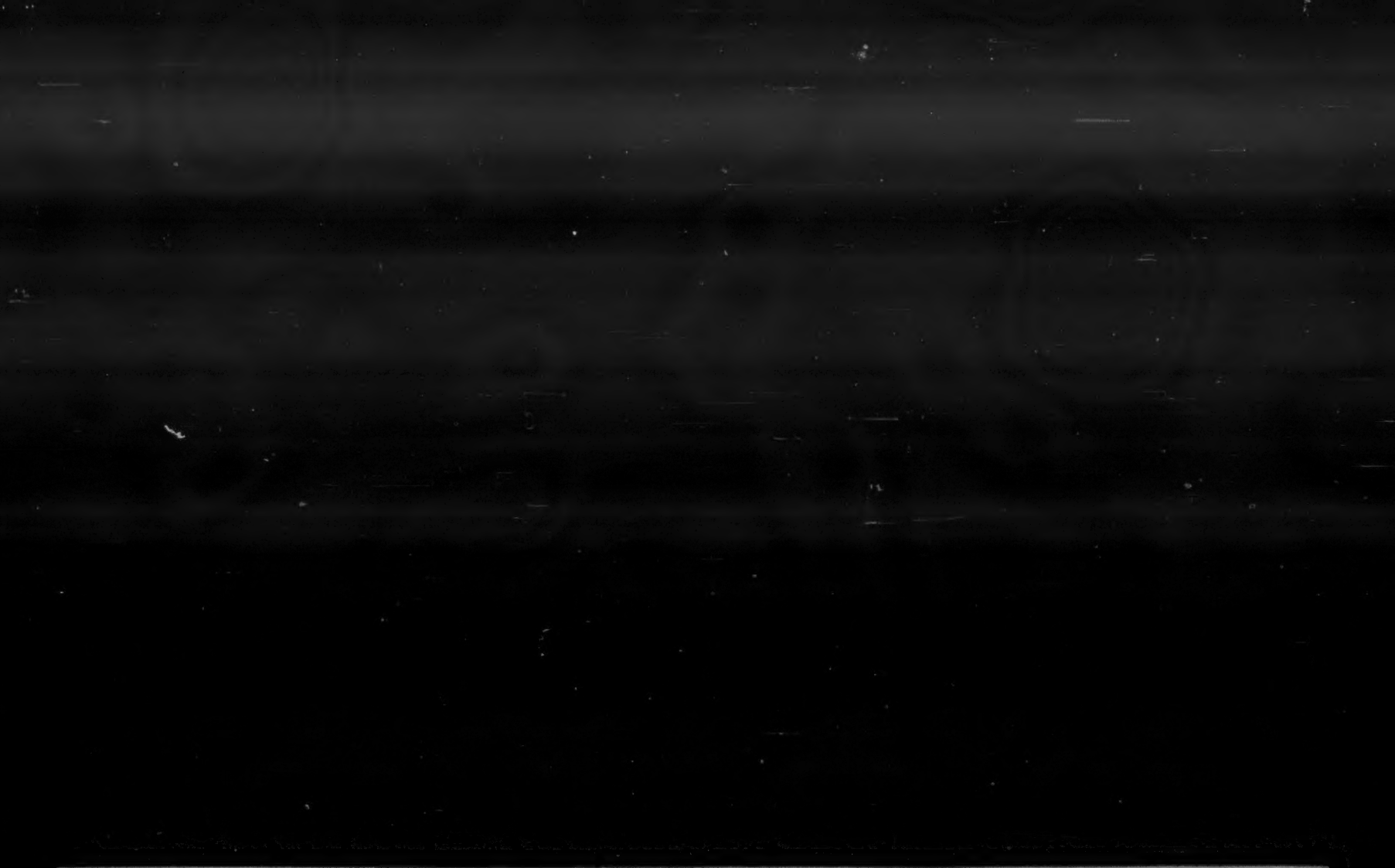
As a general, though granted superficial, review of the subject, the work fulfills its purpose well. Since this type of monograph is often used as a reference point for a more detailed probing of a particular aspect of a subject, its shortcoming is the brevity of the bibliography. Generally, the book can be recommended as an informative review.

JOSEPH S. MCLAUGHLIN, M.D.

Orthopaedic Surgery, Ed. 5. By SIR WALTER MERCER. The Williams & Wilkins Company, Baltimore, 1959.

That a book has come to a fifth edition is witness enough that it has merit. In some 20 chapters the book covers trauma as well. The author should be once again complimented on the quality and quantity of the clinical material depicted. As the author points out in his preface to the fifth edition, developments in the field of orthopedic surgery are proceeding so rapidly that it is difficult to produce a text which could be always up-to-date. It would be even more difficult to produce a text which reflected all the different schools of thought on any one particular subject within the field of orthopedic surgery.

Because of many marked differences in teaching policy between the views and opinions expressed by the author in the text and those held by many of the large teaching centers in the United States, it is felt that this book is not preferred for medical students who are attempting for the first time to learn something of orthopedic surgery in this country. However, for those already somewhat familiar with the subject matter and somewhat acquainted with the different schools, then the book has great merit in its material which can broaden the students' look at orthopedics.

The classification presented in the text is different enough in many parts from that accepted by current popular orthopedic texts in this country, strictly within the realm of pathology, as to be confusing to the new student. In the operative treatment of tuberculosis of the spine, in England, spine fusion is reserved, with few exceptions, for adult cases and not for children. It is noted that spine fusion is in high favor in the United States for this disease in children.

A. GIBSON PACKARD, M.D.